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Chiral Non-Racemic Bicyclic Lactams. Auxiliary-Based Asymmetric Reactions

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1. Introduction

The bicyclic lactam has proven to be an exceptional chiral template for the construction of a wide variety of optically pure carbocycles and heterocycles (Fig. 1). Since the first review describing the chiral non-racemic bicyclic lactam system, over 100 papers have appeared addressing its application to the construction of a variety of quaternary carbon compounds with excellent control over the absolute stereochemistry. Applications to total synthesis have effectively illustrated that the lactams can provide access to a wide variety of structural features in addition to stereogenic quaternary centers.

As a testament to its potential, notable advances continue to be made, many dealing with heterocyclic systems containing multiple stereogenic centers. The purpose of the current review is to communicate further developments of this system since it was last summarized in 1991.[1a] A short, non-comprehensive survey of bicyclic lactams was also presented in 1997.[1b]

2. Enolate Alkylation Studies: Stereoelectronic and Steric Effects

2.1. Introduction

Diastereoselective alkylations of the chiral non-racemic bicyclic lactam have provided a method for the construction of a wide variety of optically pure carbocycles and heterocycles. Detailed examples of these alkylations and their applications toward a variety of natural products have been described in a previous review.[1] A detailed mechanistic understanding of the observed diastereoselectivity, briefly addressed in the first review, has benefited greatly from extensive studies conducted over the past ten years.[2]

It has been reported that various related bicyclic (**1**–**3**) and monocyclic systems (**4**, **5**) provide high diastereofacial selectivity in alkylation reactions (Fig. 2).[3] Although this trend has been observed for some time, investigations into its origin had not been described heretofore. Concurrent studies by others[4] revealed that the facial selectivity in the

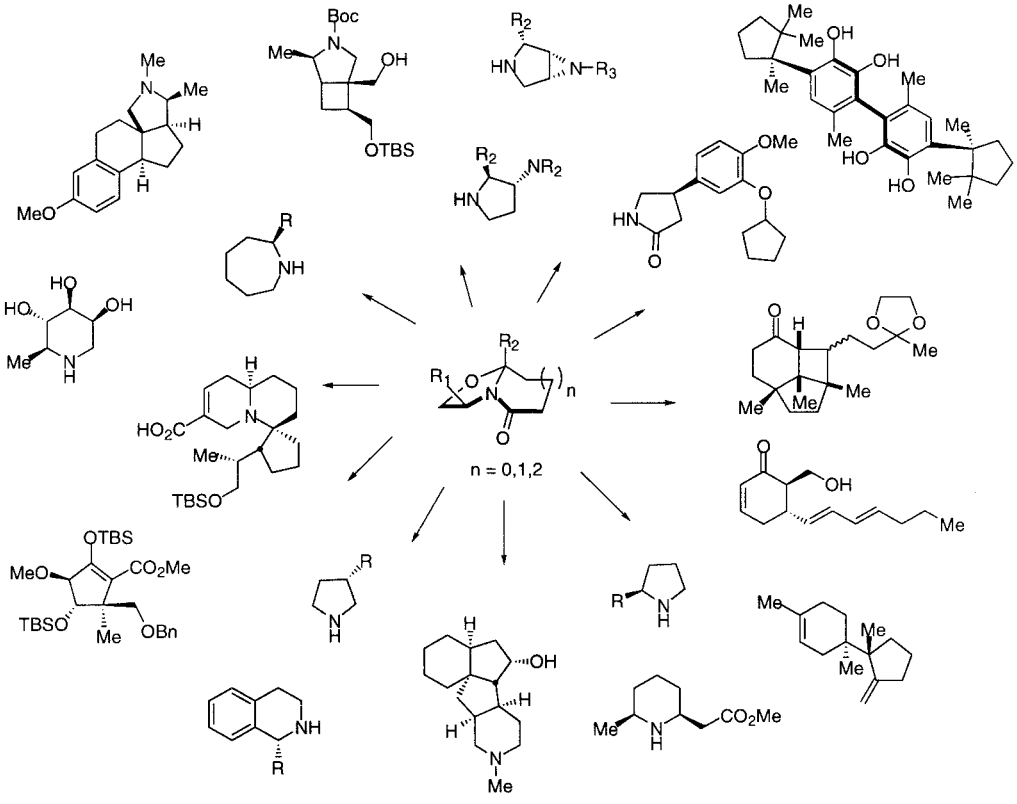


Figure 1.

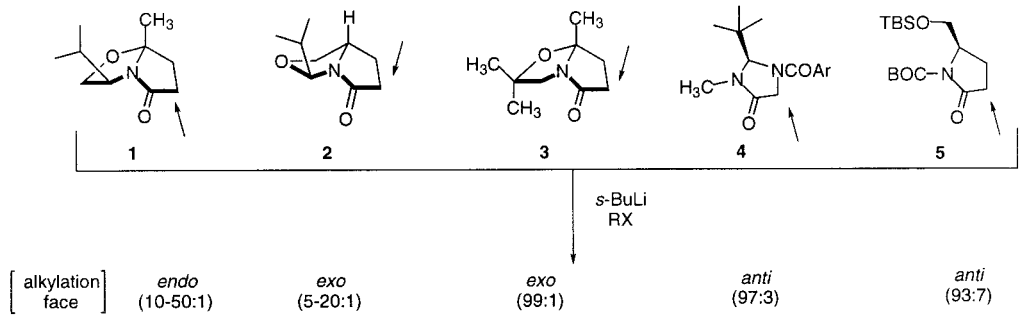
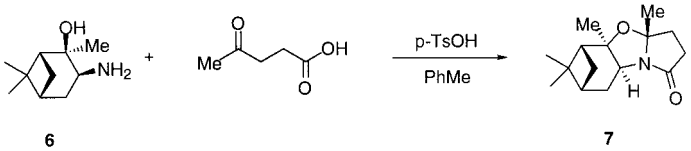
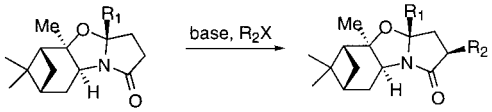


Figure 2.



Scheme 1.

Table 1. Alkylation of pinene derived bicyclic lactam **7**



Entry	R_1	R_2	R_3	Base	*T* (°C)	*Exo*:*endo*
1	Ph	Me	H	*s*-BuLi	−80	96:4
2	Ph	Me	H	LDA	25	92:8
3	Me	Me	H	*s*-BuLi	0	97:3

alkylation of [3.3.0] bicyclic lactams could be reversed by changing the structure of the chiral auxiliary. These observations initiated the search for the origin of the counterintuitive *endo* (α) selectivity obtained in the parent bicyclic lactam system **1**.

2.2. Reversal of alkylation facial selectivity

Condensation of the pinene derivative **6** with levulinic acid furnished the bicyclic lactam **7** which afforded solely the *exo* alkylation products **8** (Scheme 1).[4]

As illustrated in Table 1, alkylations leading to **8a**, **8b** occured with high *exo* facial selectivity which likely arises from a strong steric effect. The α-face of the enolate generated from **7a**, **7b** appears to be fully blocked by either the bridging *gem*-dimethyl groups of the pinene ring system or the methyl (axial) in the α-face adjacent to the ring oxygen in **7**, thus accounting for the high *exo*-selectivity at ambient temperatures (entry 2). This dramatic reversal in selectivity, when compared to the alkylation of **1**, led to a study of the structural features of other related systems and how those features might predictably affect the alkylations.

Other lactams have demonstrated a similar *exo*-selectivity, most notably, the bicyclic lactam **2** derived from pyroglutamic acid.[5] It is important to note the subtle differences between lactams **1** and **2**. The key features that seem to effect the selectivity originate in the oxazolidine ring in the bicyclic system, where the size of the group being projected into the concave face is the determining factor (these groups are highlighted in bold in structures **9**–**11**, Fig. 3). Crude models of these bicyclic lactam enolates suggest that the *endo* alkylation pathway in **10** is inhibited by the pseudoaxial hydrogen projecting in the concave region. On the other hand, enolate **9** has an oxygen in place of the methylene and therefore only projects a lone pair of electrons. These electrons may not provide sufficient steric bulk to inhibit the *endo* entry to **9**, which was, indeed, found to be the major pathway.

The addition of a large substituent on the amino alcohol moiety, as in lactam **3**, had the same effect as that of the methylene hydrogen in lactam **2**. Condensation of levulinic acid and the appropriate chiral aminoalcohol provided **3**

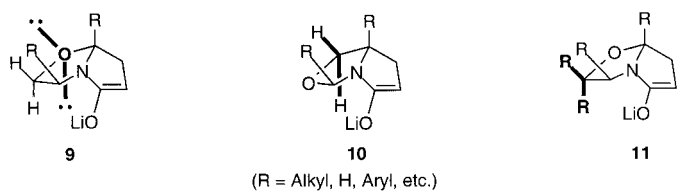
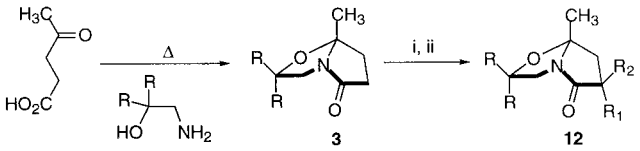


Figure 3.

Table 2. Alkylation of racemic bicyclic lactams **3**



i. *s*-BuLi, R_1X; ii. *s*-BuLi, R_2X

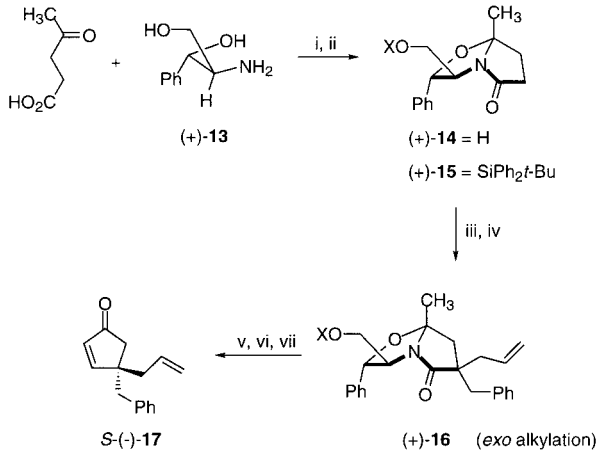
Entry	R	R_1	R_2	*T* (°C)	% Yield	*exo*:*endo*
1	Me	Bn	allyl	−78	89	99:1
2	Me	Bn	allyl	0	88	99:1
3	i-Pr	H	Bn	−78	91	96:4
4	i-Pr	Bn	allyl	−78	93	99:1
5	i-Pr	Bn	allyl	0	90	99:1
6	Ph	H	Bn	−78	94	94:6
7	Ph	Bn	allyl	−78	95	99:1
8	Ph	Bn	allyl	0	90	99:1

which was subjected to subsequent metalation/alkylation affording **12** as a single *exo* diastereomer.

As seen in Table 2, lactams containing *gem*-dimethyl, *gem*-diisopropyl, and *gem*-diphenyl all gave 94–99% of the *exo* alkyl products in the second alkylation step (the first alkylation also led to a 94:6 *exo*/*endo* ratio).

These results, using racemic lactams possessing alkyl groups on the α-face of lactams **3**, were consistent with the preliminary steric model and were confirmed by condensing the commercially available amino diol **13** with levulinic acid providing bicyclic lactam **14** (Scheme 2). The hydroxyl group was first protected as its *tert*-butyldiphenyl silyl ether (+)-**15**. Sequential metalation–alkylation with benzyl bromide and allyl bromide gave **16** with greater than 98% *exo*-facial selectivity.

Conversion of the bicyclic lactam **16** to the 4, 4-disubstituted cyclopentenone *S*-(−)-**17** and comparison with that obtained via a similar process from a valinol derived bicyclic lactam further confirmed that they possessed opposite stereochemistry.[6] *It may therefore be concluded that the presence of an alkyl or aryl group in the concave face of the oxazolidine ring completely reversed the diastereofacial selectivity.*



i. PhMe, Δ; ii. TBDPS-Cl, imid.; iii. *s*-BuLi, $PhCH_2Br$;
iv. s-BuLi, allylBr; v. Red-Al; vi. $Bu_4NH_2PO_4$; vii, KOH/EtOH

Scheme 2.

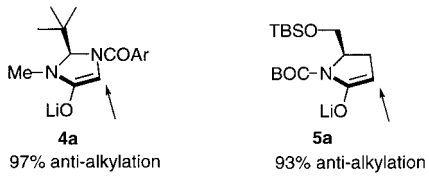


Figure 4.

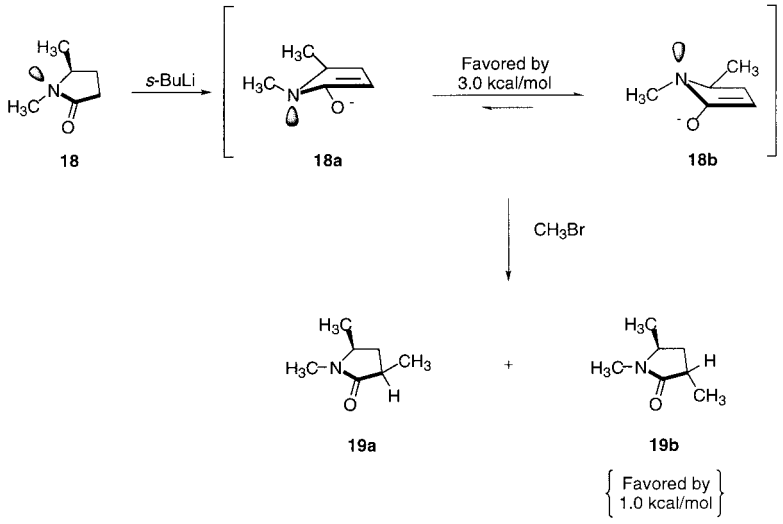
Up to this juncture, steric arguments were always proposed to explain the *endo* selectivity in the alkylation of these rigid bicyclic systems. However, analysis of the alkylation reactions of monocylic lactams **4** and **5** suggested other factors might be influencing the stereochemical outcome.

The monocyclic enolates derived from imidazolidinones **4a**[3a] and 2-pyrrolidinones **5a**[3b] are devoid of any polycyclic concave/convex faces, yet exhibited high degrees (>95%) of facial selectivity when their enolates were alkylated (Fig. 4). In each of these cases, alkylation took place *anti* to a relatively large substituent, which could be due to steric factors. Seebach[3a] has suggested a stereoelectronic effect in **4a**, based on the slight pyramidalization of the enolate β-carbon. Additionally, there has been a report[7] on lactam alkylations where the stereochemical result was due to the bulk created by chelation of the metal ion on the enolate to the ligands present in the lactam. Furthermore, the notion that the lone pair on nitrogen exhibited some electronic effect on the diastereofacial selectivity has been suggested by several authors, with no supporting evidence.[8]

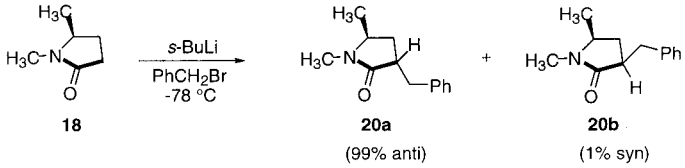
In order to isolate the potential electronic aspect of lactam alkylations, ab initio calculations were conducted on the simple pyrrolidinone system **18** (Scheme 3). It was determined that of the two lowest energy enolates **18a/18b**, the latter was favored by 3 kcal/mol due to strong 1, 2- interaction of the two methyl groups in **18a**.[2a–c] Determination of the S_N2 transition state energies for alkylation of enolate **18b** with methyl bromide revealed that *anti*-facial entry was favored over *syn*-facial entry by 0.99 kcal/mol. Thus, **19b** was predicted to be the preferred product of alkylation over **19a** by a ratio of 5.3:1 (25°C). Additionally, it was evident by inspection of the HOMO that the larger coefficient found on the π-bond was *anti* to the nitrogen lone pair, and therefore lay on the α-face of the lactam enolate.

For further support of the stereoelectronic effect, previously observed, the commercially available (±)-1,5-dimethylpyrrolidinone **18** was converted to its enolate (*s*-BuLi, THF, −78°C) and treated with benzyl bromide to give the *anti* alkylated product **20a** in >99:1 *anti*/*syn* ratio (Scheme 4), thus providing further experimental support for the ab initio calculations mentioned above.

The combination of experimental and computational studies that were performed indicated that the observed *endo* selectivity may originate from a heretofore undetected electronic effect of the nitrogen lone pair perturbing the HOMO of the enolate. However, this relatively small stereoelectronic effect could apparently be overcome by steric and/or other



Scheme 3.



Scheme 4.

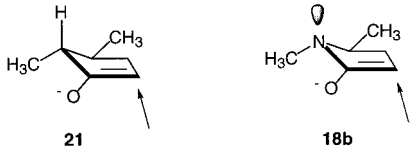


Figure 5.

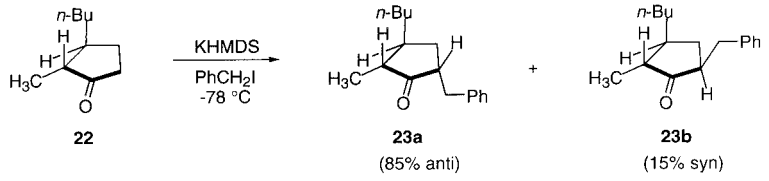
undetectable factors. One of these other possible factors, as suggested by Houk,[2d] could be torsional and steric effects. Houk has shown that the stereoselectivity may be influenced by torsional strain and steric interactions.[9] He has also shown that distortions of π-orbitals can result from torsional effects,[10] and has performed similar calculations on *trans*-2,3-dimethylcyclopentanone **21** as those done in the author's laboratory on lactam **18b** (Fig. 5). In this molecule, where the nitrogen has been replaced by carbon, ab initio calculations predicted a 1.0 kcal/mol preference for α-attack on the enolate. This difference is in accord with torsional strain differences in allylic carbon–hydrogen bonds.

In order to find experimental support for this prediction, *trans*-3-butyl-2-methylcyclopentanone **22** was synthesized, subjected to kinetic enolate generation and quenched with benzyl iodide.[2d] ^{1}H NMR analysis revealed that the *endo* product **23a** was favored (85:15) which was in agreement with Houk's computational prediction (Scheme 5).[2d]

Although these diastereofacial selectivity studies on the alkylation of mono- and bicyclic lactams have provided some insight into the subtleties that influence the stereocontrol of enolate alkylations, further studies are still necessary. Stereoelectronics, torsional angles and sterics all influence this process with varying degrees of stereocontrol. Even though none of these effects has been found solely responsible for the high selectivity, their effects are certainly not mutually exclusive.

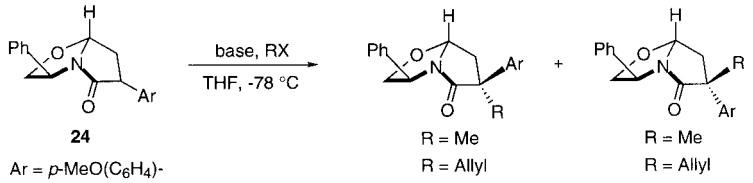
2.3. Alkylation of angular hydrogen bicyclic lactams

Studies on the alkylation of the angular hydrogen bicyclo [3.3.0] system revealed that the selectivity was significantly lower when compared to the angular methyl derivative. Since the nature of the leaving group in the electrophile had previously received little attention, alkylations of **24**

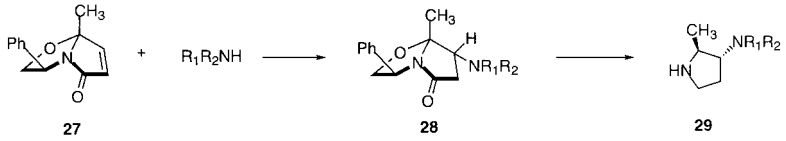


Scheme 5.

Table 3. Alkylations of angular hydrogen lactam **24**



Entry	Base	RX	Time	Yield (%)	*endo*/*exo*
1	LHMDS	MeI	1 h	94	86/14
2	LHMDS	MeOTf	20 min	99	95/5
3	LHMDS	MeOTs	14 h	74	94/6
4	KHMDS	AllylBr	15 min	99	83/17
5	KHMDS	AllylOTs	30 min	97	90/10



Scheme 6.

with other methyl and allyl electrophiles were examined.[11] The selectivity increased from ~6:1 to >20:1 when the electrophile was changed from methyl iodide to methyl trifluoromethanesulfonate (Table 3, entries 1–3). The allyl derived electrophiles had an equally significant increase in selectivity (from ~5:1 to 10:1) when the bromide leaving group was exchanged with *p*-toluenesulfonate (Table 3, entries 4, 5).

This change in selectivity may be explained by a better match between the hardness of the lithium or potassium enolate and the electrophile. Alternatively, the presence of the Lewis basic oxygens in the sulfonate moiety may act as a ligand for pre-organization of the lithium or the potassium enolate with the electrophile prior to bond formation, thus increasing selectivity.

3. Conjugate Additions

The first report on conjugate additions to the bicyclic lactams[1,12] included cyclopropanations via the addition of sulfoxonium ylides. Since then, conjugate additions to these systems have been extended to include several other reaction types summarized below.

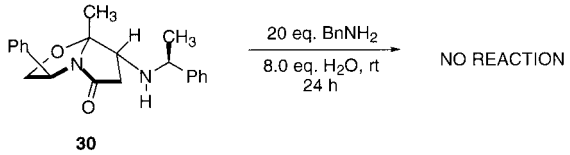
3.1. Amines conjugate addition

Additions of amines to the α,β-unsaturated lactam **27** were found to occur with high facial selectivity (Scheme 6). These reactions were applied to the synthesis of several 3-aminopyrrolidines found in various biologically significant compounds (Fig. 6, **25** and **26**).[13]

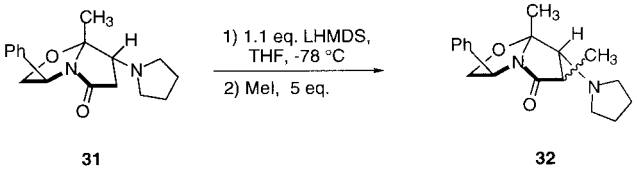
Two key features were found to be necessary for efficient amine addition: (a) the presence of water was essential in order to drive the amine addition to completion, and (b) complete reaction required 8 equiv. of the amine.

It was also found that the product of the amine addition to the lactam appeared to be kinetically controlled and highly resistant to reversal. Thus, thermodynamic factors were not involved. This was further shown when no amine exchange took place when **30** was subjected to scrambling conditions (Scheme 7).[14]

In order to ascertain whether generation of the enolate would result in reversal of the amine addition, pyrrolidino lactam **31** was subjected to lithium hexamethyldisilazide (−78°C) and treated with excess iodomethane (Scheme 8). Only the methylated lactam **32** was formed as a 2:1 mixture of α- and β-diastereomers in the 2-position.



Scheme 7.



Scheme 8.

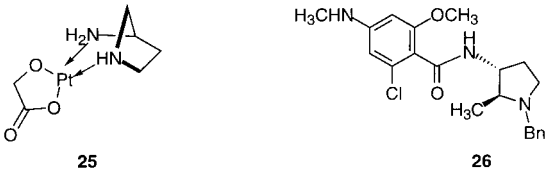
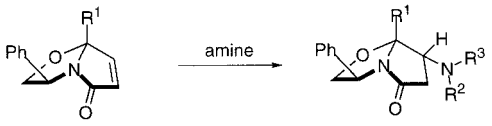


Figure 6.

Table 4. Conjugate addition of amines to unsaturated bicyclic lactams **33**



33 **37**

Entry	R^1	Amine	Yield (%)	Product	d.r.
1	Me	$PhCH_2NH_2$	84	**37a**	95:5
2	Me		83	**37b**	95:5
3	Me		85	**37c**	95:5
4	Ph		89	**37d**	>98:2
5	Me		89	**37e**	>98:2

As the steric bulk of the amine was increased (changing to a secondary amine), the selectivity of *endo–exo* addition increased from 19:1 to >98:2 (Table 4). Thus, bulkier nucleophiles were seemingly sensitive to facial selectivity (Entries 1, 5). Similarly, when the angular substituent of the lactam was changed from methyl to phenyl (Entries 2 and 4), the selectivities from the reaction with the same primary amine changed from 19:1 to >98:2.

Increasing the size of the angular substituent (R^1) resulted in increased interaction with the incoming amine component on the *exo* face. On the other hand, increasing the steric bulk of the amine (R^2 or R^3) also caused increased steric interaction with the angular substituent on the *exo* face thus favoring *endo* entry. That these steric effects were so critical to the stereochemical outcome suggested strongly that the addition process leading to the amino lactams may have proceeded through a late (product-like) transition state (Fig. 7).

3.2. Aziridination by conjugate addition

The amine conjugate addition, described above, was extended to construct the aziridine moiety with high efficiency.[14] Simply modifying the α,β-unsaturated bicyclic lactam **33** to include a leaving group at the α-carbon, i.e. iodide, provided an intramolecular reaction pathway for formation of the aziridine. This α-iodo-α,β-unsaturated lactam **38** was treated with a primary amine furnishing the aziridine **39** in good to excellent yields. The aziridinolactams **39** were readily reduced to their corresponding chiral 2-alkyl-3,4-aziridinopyrrolidines **40** (Scheme 9). It was also observed that the 2-substituent of the product **41** had been stereochemically modified (inverted) from its original position in the aziridinolactam **39**. This was attributed to the presence of the aziridine ring hindering attack of hydride from the underside of **39**.

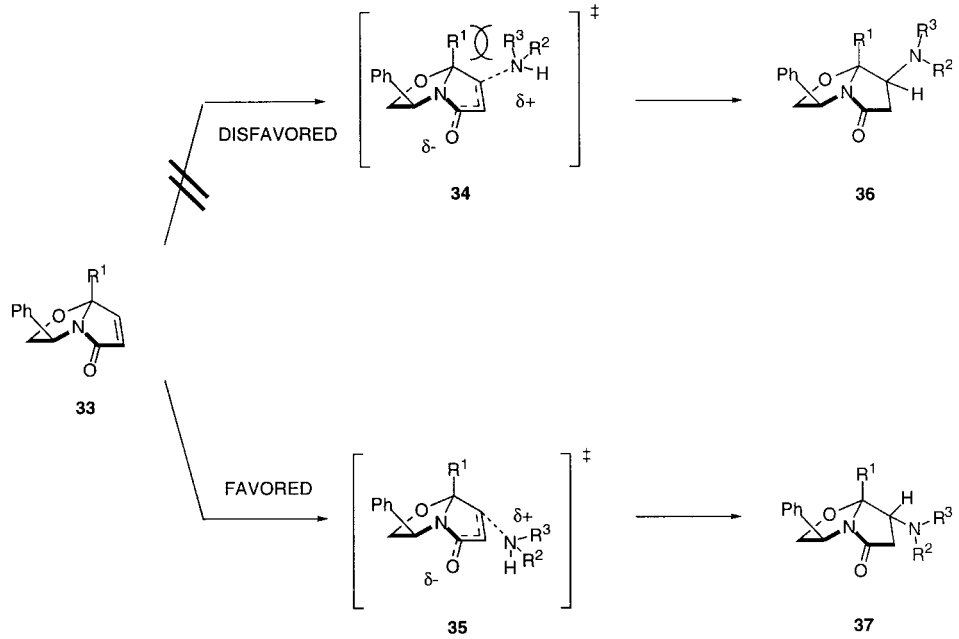
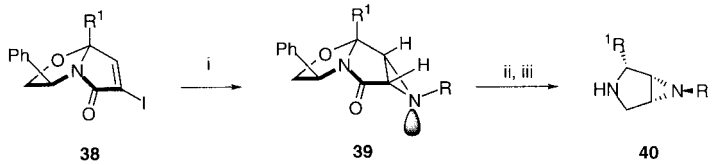
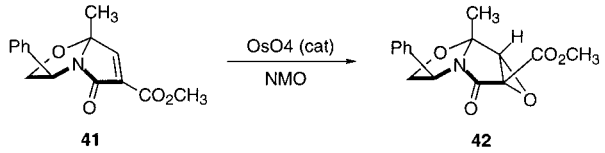


Figure 7.



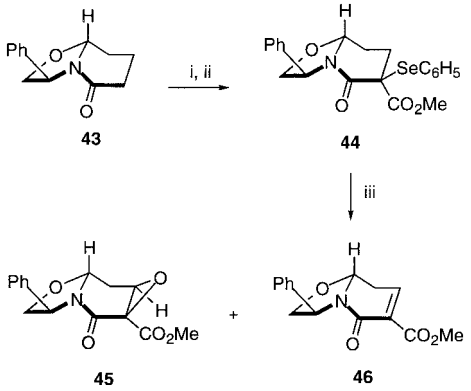
i. RNH_2; ii. AlH_3; iii. $Pd(OH)_2$, H_2

Scheme 9.



41 42

Scheme 10.



43 44 45 46

i. LiHMDS, $ClCO_2Me$; ii. $BrSeC_6H_5$; iii. *m*-CPBA

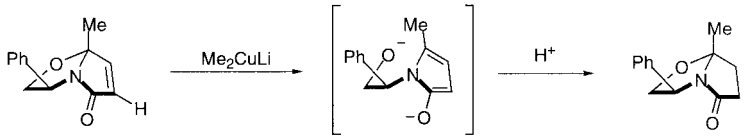
Scheme 11.

unsaturated system with *m*-CPBA. Here again, the angular substituent seems to dictate the facial selectivity. The presence of an angular hydrogen allowing for β-epoxidation where the oxidation of the intermediate selenide was accomplished with ozone, only the corresponding α,β-unsaturated lactam **46** was isolated.

3.4. Organocuprate conjugate addition

The implementation of cuprate additions to electrophilic olefins has only been rarely utilized in a chiral sense.[18] Attempts at addressing this task involved the addition of organocuprates, in a diastereoselective fashion, to the bicyclic lactam **47**. Initial attempts to add simple Gilman-type cuprates[19]to the bicyclic lactam resulted in rapid reduction of the enone system furnishing the saturated lactam **48** (Scheme 12).

Previous studies[20] from this laboratory described Diels–Alder cycloaddition to **47** as being unsuccessful. Only when a carboalkoxy group was introduced in the α-position did reaction occur. It was subsequently found that the standard 'Gilman reagent' added to lactam **49** providing the β-substituted lactam **50** in a 3:1 *trans*/*cis* diastereomeric ratio. Further efforts showed that the addition of a lower



47 48

Scheme 12.

3.3. Epoxidation by conjugate addition

The addition of oxygen to the α,β-unsaturated lactam **41** was also described using tertiary amine *N*-oxides.[15] Using the Upjohn process for the dihydroxylation of unsaturated systems (catalytic OsO_4, *N*-methylmorpholine oxide), the α-epoxide **42** was isolated in high yield rather than the expected diol (Scheme 10). Again, the stereochemical outcome of this reaction was consistent with the substituents present on the β-face blocking approach and favoring α-face entry.

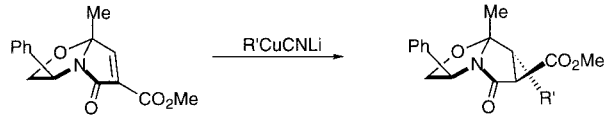
It was found that osmium tetroxide was unnecessary and NMO could be substituted with trimethylamine-*N*-oxide.[16] The α-facial epoxidation was successful only with a variety of doubly activated α,β-unsaturated bicyclic lactams with yields ranging from 90–99%.

Epoxidation of the α,β-unsaturated lactam has not been limited to the bicyclo[3.3.0] system. Amat[17] has shown that one can use the [4.3.0] bicyclic lactam **43** to obtain the α,β-epoxy lactam **45** by treatment of the α-selenyl bicyclic lactam **44** with *m*-CPBA (Scheme 11).

The epoxidation presumably resulted from the formation of the selenoxide of **44** which eliminated to the α,β-unsaturated lactam **46**. This was followed by epoxidation of this order cyanocuprate produced a >95:5 ratio of diastereomers (Table 5). The dominant *endo* addition by the cuprate may also be attributed to the presence of the angular methyl group which interferes with the approach of the cuprate on the β-face.

The obvious disadvantage of using a carbomethoxy group in **49** as a 'conjugate addition activator' was its removal after the addition. When alkaline hydrolysis was employed to decarboxylate **50c**, rapid epimerization was noted. A plausible route to the destruction of the stereogenic center in **51** is illustrated in Scheme 13.

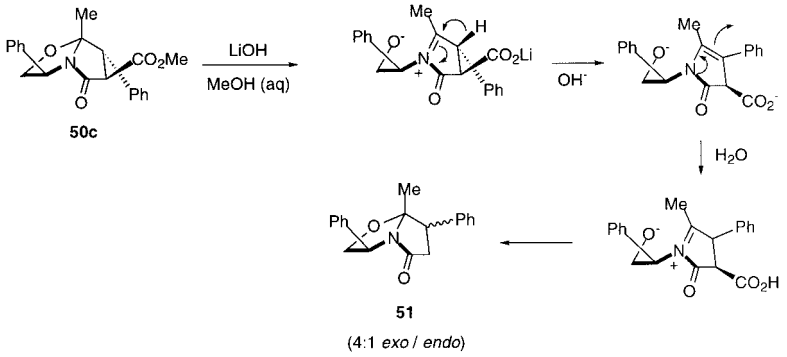
Table 5. Conjugate additions of organocuprates to **49**



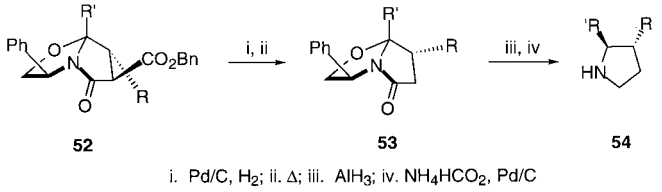
49 50 a-d

Product	R′	Yield (%)[a]
50a	Me	84
50b	vinyl	84
50c	phenyl	76
50d	*n*-butyl	80

[a] The d.r. of all the products was >95:5 as determined by ^1H NMR.



Scheme 13.



Scheme 14.

The base induced pathway leading to epimerization was ultimately prevented by changing to a benzyl ester, which could be easily removed via hydrogenolysis, then decarboxylation to **53** in refluxing toluene (Scheme 14). All that remained to reveal the pyrrolidine system **54** was reductive removal of the auxiliary.

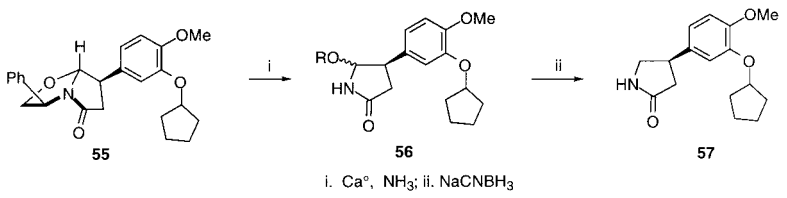
This sequence was then applied to the synthesis of the antidepressant and phosphodiesterase inhibitor, Rolipram® **57** (Scheme 15).[21] The synthetic route[21] included the conjugate addition of the appropriate arylcuprate and removal of the ester to form **55**. This was followed by reductive removal of the chiral auxiliary to afford the carbinolamide **56** which was converted to Rolipram® **57**.

Biologically important piperidines have also been constructed using the chiral bicyclic lactam template. The total synthesis of (+)-femoxetine **66a** and (+)-paroxetine **66b** was realized by the addition of the appropriate cuprate to an α,β-unsaturated [4.3.0]-bicyclic lactam **60** (Scheme 16).[22] In order to access the more electrophilic Michael acceptor, an electron-withdrawing substituent was installed. The requisite arylcuprate was added to the crude mixture to afford the Michael addition product **61** in excellent diastereoselectivity (97:3). Reduction with alane gave the piperidine **62** which was converted to the *t*-butyl carbamate **63** via hydrogenolysis of the auxiliary with in situ protection. Femoxetine **66a** and paroxetine **66b** were obtained by mesylation of the hydroxymethyl group and displacement with the appropriate benzyl alkoxide. Treatment of the carbamate with lithium aluminum hydride furnished femoxetine **66a** and treatment of the corresponding precursor with trifluoroacetic acid produced paroxetine **66b**.

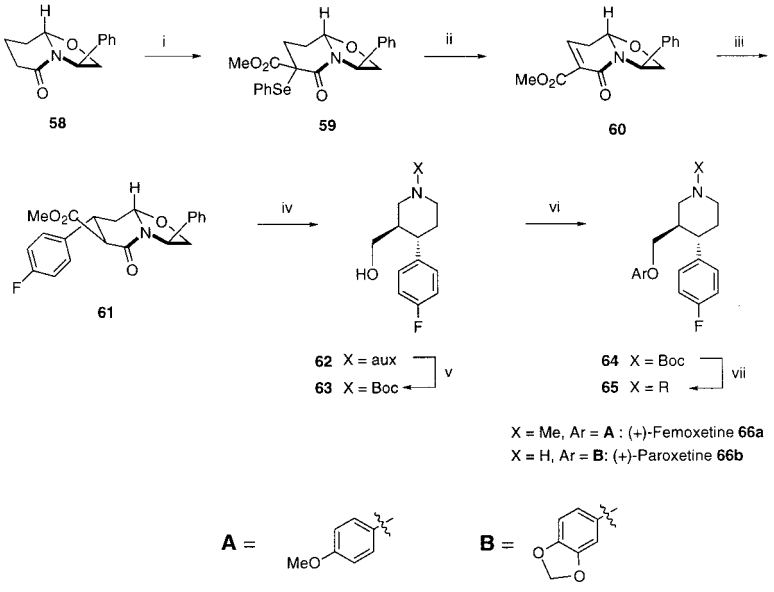
3.5. Allylsilane addition (cyclobutannulation and cyclopentannulation)

The use of simple allylsilanes in cyclopentane annulations is a relatively new area of research in organic chemistry.[23,24] Allylsilanes have been primarily utilized in Lewis acid mediated Sakurai reactions with both aldehydes and electron deficient olefins.[25] Bicyclic lactam investigations in this area utilized the Lewis acid mediated addition of allyltriisopropylsilane to an α,β-unsaturated system **67** (Scheme 17).[26]

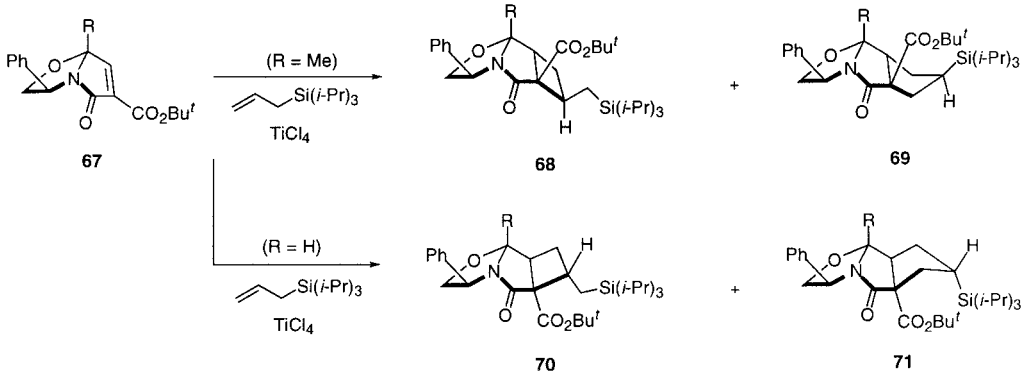
Although the existence of a [2+2] pathway under these reaction conditions has been questioned, cyclobutane products (**68**, **70**) were unambiguously identified through two dimensional NMR experiments and X-ray crystallography. These results were the first *confirmed* examples of allylsilanes undergoing Lewis acid mediated cyclobutannulation with electron deficient olefins.



Scheme 15.



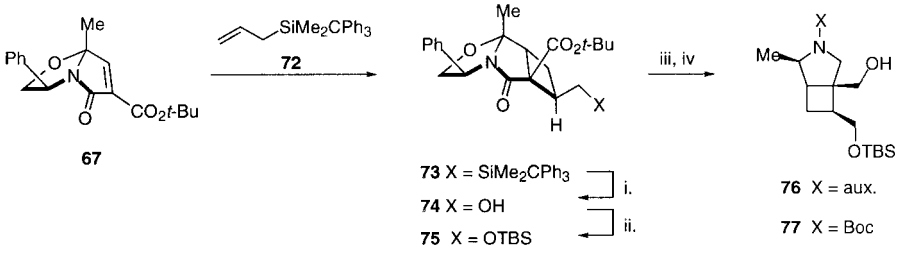
Scheme 16.



Scheme 17.

In order to extend this technique and exploit the dual reactivity of the allylsilanes, the use of the silicon atom as a hydroxyl surrogate was investigated.[27]

A novel allylsilane **72** to satisfy the above conditions, was employed in the construction of optically pure heterocycles using the bicyclic lactam template (Scheme 18). Addition to the α,β-unsaturated bicyclic lactam **67** occurred under Lewis acid mediated conditions to provide the cyclobutane adduct **73** in moderate yield. Tamao–Fleming oxidation occurred in moderate yield to furnish alcohol **74**, which was protected as its *tert*-buyl-dimethylsilyl ether **75**. Lactam **75** was then reduced with diisobutylaluminum hydride and protected to provide a single diastereomer of the conformationally constrained cyclobutano[c]pyrrolidine **77**.



Scheme 18.

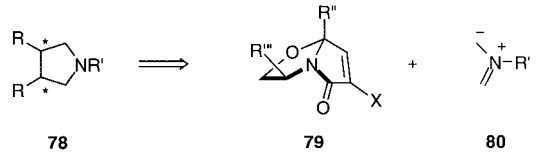
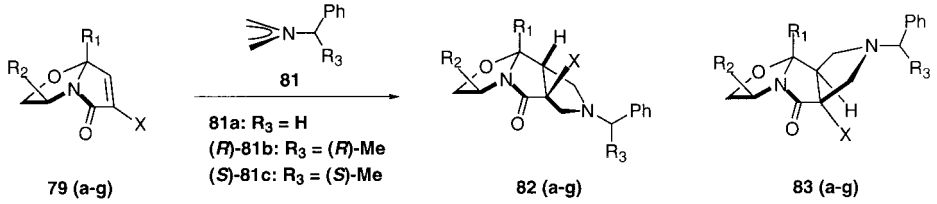


Figure 8.

the selectivity is very sensitive to the presence of α-substituents (R_1) larger than hydrogen where substantial matched and mismatched double diastereoselectivity was observed. Based on these data, experimental and computational studies of other azomethine ylide cycloaddition reactions, a predictive model was developed which assisted in further optimization of the selectivity (Fig. 9).

Table 6. Effect of structure on facial selectivity



Entry	Lactam **79**			Lactam	Ylide **81a**	Ylide (*R*)-**81b**	Ylide (*S*)-**81c**
	R_2	R_1	X		**82:83**	**82:83**	**82:83**
1	*i*-Pr	Me	H	**79a**	91:9	94:6	91:9
2	Ph	Me	H	**79b**	94:6	91:9	92:8
3	Ph	H	H	**79c**	17:83	19:81	16:84
4	*i*-Pr	Me	CO_2Me	**79d**	71:29	87:13	59:41
5	*i*-Pr	Me	CO_2t–Bu	**79e**	72:28	92:8	51:49
6	*i*-Pr	Ph	CO_2Me	**79f**	74:26	87:13	69:31
7	Ph	Me	Br	**79g**	96:4	>98:2	91:9

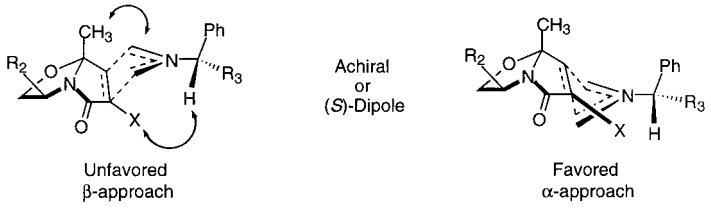


Figure 9.

4. Pericyclic Reactions

4.1. Azomethine ylide [3+2] cycloadditions. Formal synthesis of (+)-conessine

The 1,3-dipolar cycloaddition reactions of azomethine ylides **80** have been extensively reviewed,[28] and the basic reaction has been studied as both it's racemic and asymmetric variants.[29] The use of the chiral bicyclic lactam **79** as a chiral dipolarophile has also proved to be quite versatile (Fig. 8).

It was found[30] that the size of the angular substituent (Table 6, R_1, **79**) exhibited a significant effect on the *endo*/*exo* selectivity in the cycloaddition. This was in agreement with previous studies[13,17,23] of other cycloadditions (Diels–Alder) and conjugate additions on these lactams.

Table 6 illustrates the existence of a steric effect with respect to the substituent α to the carbonyl in the dipolarophile (lactams **79a**–**g**). As seen in entries 1 and 2, there was very little difference in selectivity when the azomethine ylide was achiral or derived from the optically pure α-methyl benzylamine. Entries 4–6 demonstrate that

The steric model developed provided insight for the rational control of stereoselection in the dipolar cycloadditions of simple azomethine ylides to a structurally variable chiral template. This reaction route was employed in the formal synthesis of (+)-conessine **84**, a steroidal alkaloid possessing significant biological activity (Fig. 10).[31] The synthesis of **85** is outlined in Scheme 19.

4.2. [2+2] Cycloadditions. Synthesis of the core of (−)-lintenone

Pericyclic reactions employing the bicyclic lactam as a chiral dienophile or dipolarophile have proven very successful in the construction of carbocycles and heterocycles as

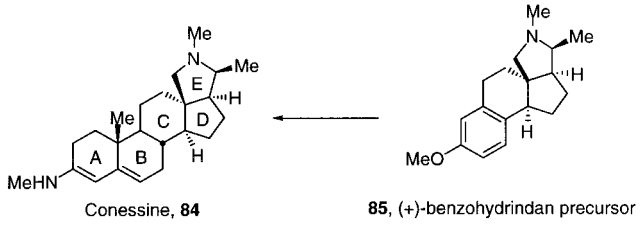
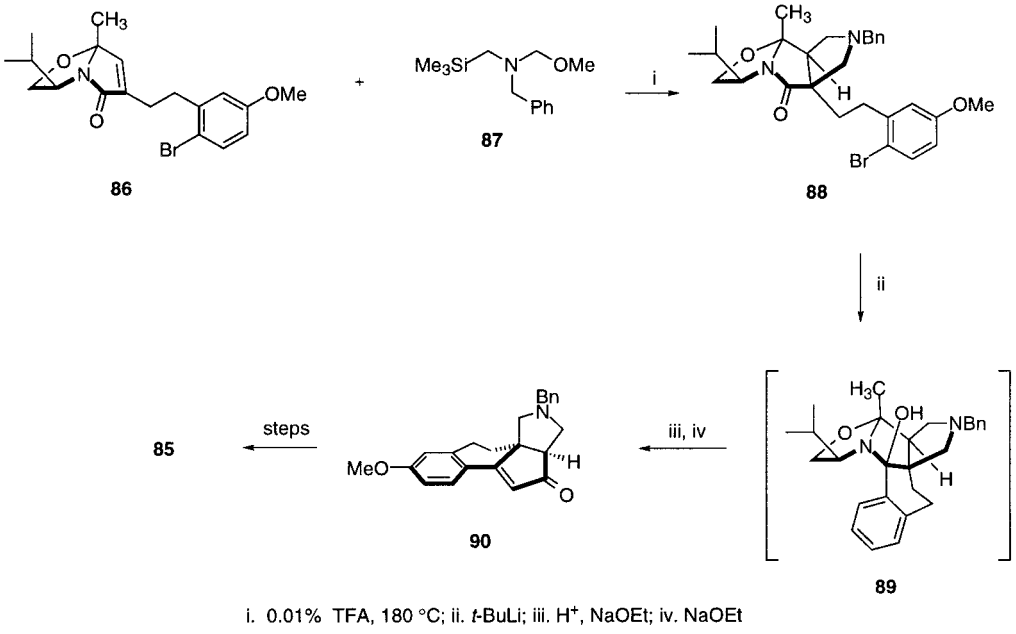
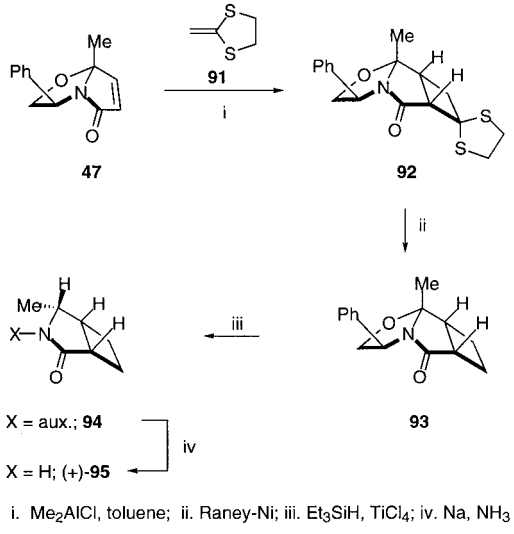


Figure 10.



Scheme 19.

seen above. Chiral cyclobutanes were readily obtained by Lewis acid mediated addition of dithioketals to unsaturated bicyclic lactams or by photochemical manipulation of the lactam produced compounds.



Scheme 20.

The dithioketal, methylenedithiolane **91** proved to be an excellent cycloaddition partner for the [2+2] reaction.[32] Treatment of lactam **47** with dimethylaluminum chloride and dithiolane **91** gave 92% of the cyclobutane adduct **92** as a single diastereomer (Scheme 20). Raney–nickel reduction afforded the cyclobutano lactam **93** which was converted to the optically pure cyclobutano γ-lactam **95** in two steps.

Rationalization for the unusual stereochemical outcome in the reduction may be represented by the structures shown in Fig. 11. The configuration of the phenylglycinol moiety, the complexation of the oxophilic titanium salt, and the presence of the *endo*-fused cyclobutane ring all appear to block the α-face to nucleophilic hydride delivery. Thus, entry of hydride from the β-face provides the inverted position taken by the methyl group which was confirmed by X-ray data.

The [4.3.0] bicyclic lactam **104** was also employed to construct an optically pure 4,4-disubstituted cyclohexenone **98** which underwent an intramolecular photochemical [2+2] cycloaddition reaction to construct the tricyclic carbon skeleton of (−)-lintenone **99**[33] (Fig. 12).

Synthesis of the requisite chiral, non-racemic cyclohexenone **98** was accomplished by dialkylation of bicyclic lactam **104** affording a 7:1 mixture of alkylated products **97**

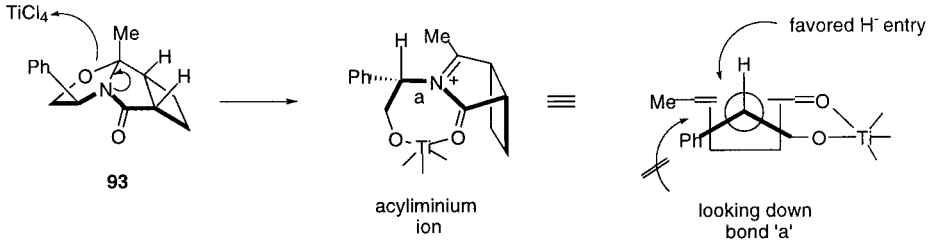


Figure 11.

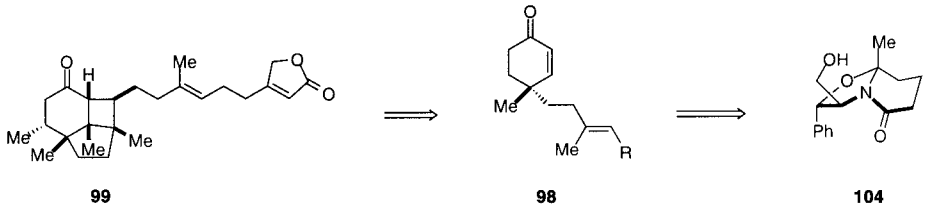
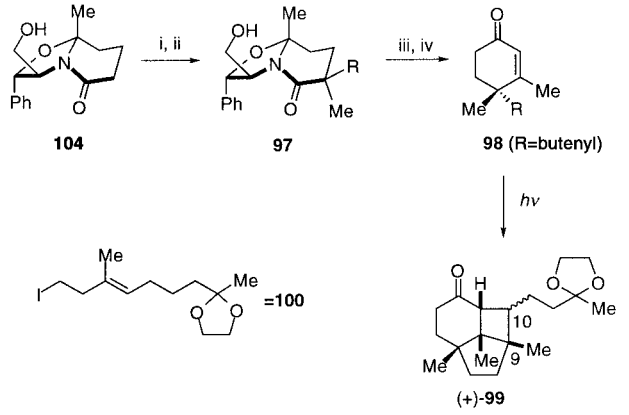


Figure 12.

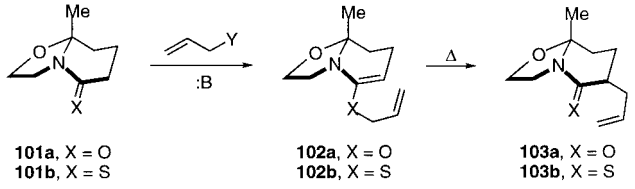
with *endo* entry at each alkylation step being the predominant pathway (Scheme 21). The chiral auxiliary was removed by addition of methyllithium to the lactam carbonyl then hydrolysis under anhydrous conditions to provide the 4,4-disubstituted cyclohexenone **98**. Cyclohexenone **98** was irradiated to produce the photo [2+2] adduct (+)-**99**. The cycloaddition proceeded in high yield albeit in low diastereoselectivity at C-10 (1.4:1). Cycloadditions in similar systems lacking the C-9 methyl group led to much higher selectivity (up to 9:1). It was concluded that the stereochemical outcome of the cyclization must be strongly perturbed by the presence of the C-9 methyl group.

4.3. Thio-Claisen [3,3] rearrangements. Synthesis of (−)-trichodiene

The thio-Claisen rearrangement (**102b→103b**), although potentially a powerful synthetic tool, has garnered relatively little attention compared to its well-known oxygen analog (**102a→103a**) (Scheme 22).[34] Conversion of the bicyclic lactam **101a** to the thio-lactam **101b** was accomplished by treatment with either Belleau's or Lawsson's reagent.[35]



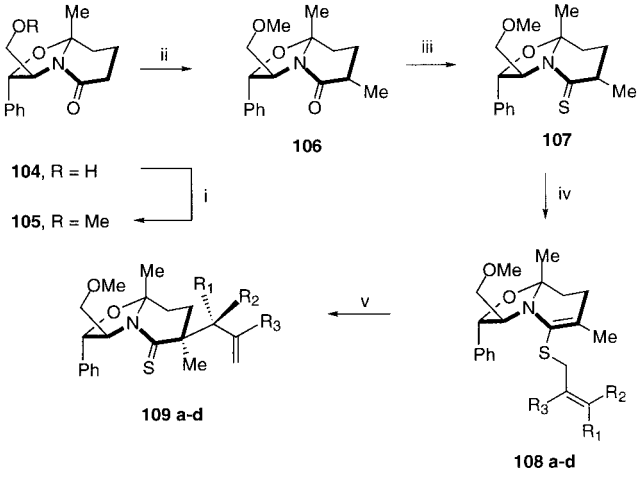
Scheme 21.



Scheme 22.

S-Alkylation was accomplished by trapping the thioenolate of **107** with the appropriate allylic halide followed by stirring at ambient temperatures or heating in an appropriate solvent (Scheme 23). The stereochemistry of the rearrangement was confirmed by single crystal X-ray analysis of **109b** obtained from the crotyl thioether **108b** (Table 7). The X-ray study clearly indicated that the allyl groups in **109** had entered from the *exo* (β) face of the bicyclic system. This stands in contrast to earlier studies, wherein enolate-based alkylation on the amide preferred the *endo* (α) face. In addition to rearrangement on the *exo* face, the product stereochemistry in the allylic position appeared to be the result of a chair transition state, **111** (Fig. 13).

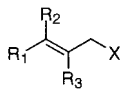
In order to gain insight into the origin of this stereochemical outcome, a variety of other auxiliaries were investigated (**112a–d**, Table 8) as well as the introduction of Lewis acids.[34d,e] An interesting remote steric effect was observed in the reactions with various chiral auxiliaries. The original thio-Claisen rearrangement was performed on bicyclic



Scheme 23.

Table 7. Diastereoselective thio-Claisen rearrangements (**108→109**)

110 =



Entry	Allyl halide **110** R_1	R_2	R_3	X	*T* (°C)	% **109**	d.r
a	H	H	Me	Cl	25	71	3:1
b	Me	H	H	Br	25	79	91:9
c	Ph	H	H	Br	140	49	>99:1
d	Me	Me	H	Br	149	68	>99:1

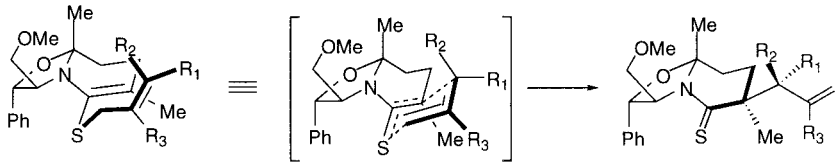
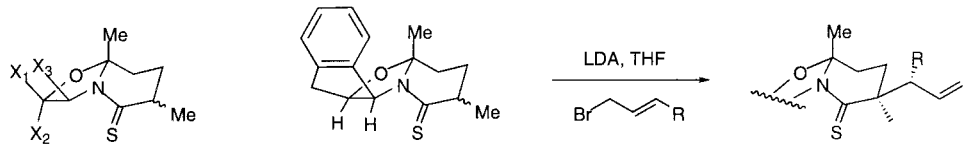


Figure 13.

Table 8. Thio-Claisen rearrangement on various bicyclic lactams **112**



112a : X_1 = H, X_2 = Ph, X_3 = CH_2OMe
112b: X_1 = Ph, X_2 = H, X_3 = Me
112c: X_1 = Me, X_2 = Me, X_3 = Ph

112d **113a-d**

112	X_1	X_2	X_3	R	T (°C)	Yield	Additive	d.r. (**113**)
a	H	Ph	CH_2OMe	Me	140	48	–	99:1
b	Ph	H	Me	Me	65	70	–	64:36
c	Me	Me	Ph	Ph	110	52	–	>95:5
d	–	–	–	Me	65	40	–	50:50
a	H	Ph	CH_2OMe	Me	25	58	$Pd_2(dba)_3$	82:18
a	H	Ph	CH_2OMe	Me	25	58	$NiCl_2(PPh_3)_2$	80:20

lactam **112a** which places the phenyl substituent in the concave (*endo*) face of the oxazolidine. Two other auxiliaries (**112b** and **112d**, Table 8) which lack the substituent in the concave face (nor-ephedrine and amino-indanol) provided very poor diastereoselectivity.

Based on the data obtained from these various auxiliaries, it is believed that the key steric factor in determining the selectivity is the group X_2 in the concave face of **112**. If X_2=H, the diastereoselectivity quickly falls to nearly 1:1.

Transition metal catalysis provided a mild entry into the desired rearrangement product. Addition of palladium(II) salts (10 mol%) to the *N*,*S*-ketene acetal **112c** gave the rearranged product at room temperature with a much higher isolated yield than the original reaction conditions.[34e]

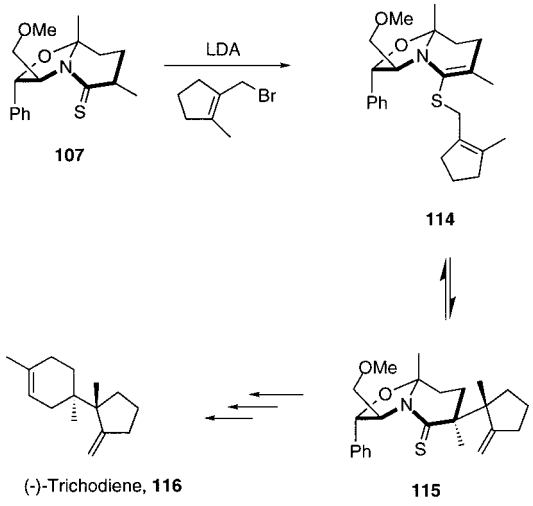
The thio-Claisen reaction was applied to the synthesis of several cyclohexenone derivatives including the first synthesis of the sesquiterpene, trichodiene[34b] (**116**) in enantiomerically pure form. The latter contains the difficultly accessible vicinal quaternary stereogenic center (Scheme 24). The key transformation in this synthesis was the installation of the vicinal quaternary centers into **115** in a single operation via *S*-alkylation and subsequent thio-Claisen rearrangement.

5. Chiral Bicyclic Thiolactams

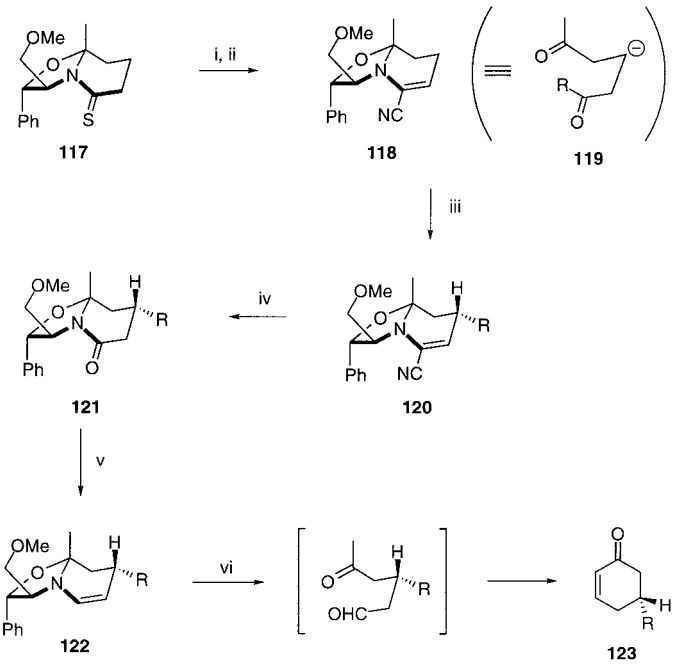
The bicyclic thiolactam has also been used in at least two other reaction manifolds that have provided access to optically pure heterocycles and carbocycles. In the first case, the bicyclic lactam may exhibit properties of a bis-homoenolate **119**.

5.1. Cyano-enamine alkylations: synthesis of (−)-penienone

Conversion of bicyclic lactam **117** to the *N*,*S*-ketene acetal followed by treament with potassium cyanide and cuprous iodide furnished the bicyclic cyano-enamine **118** (Scheme 25). A metalation/alkylation sequence followed by acid hydrolysis led to the alkylated product **121** in high yield with excellent facial stereocontrol (>95:5).[36]



Scheme 24.



i. Et_3OBF_4; ii. KCN, CuI, cat. I_2; iii. LiTMP, R-X; iv. HCl, THF/H_2O; v. DIBALH•*n*-BuLi; vi. H_3O^+

Scheme 25.

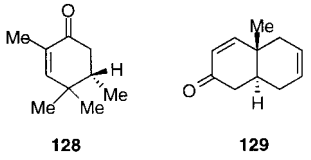


Figure 14.

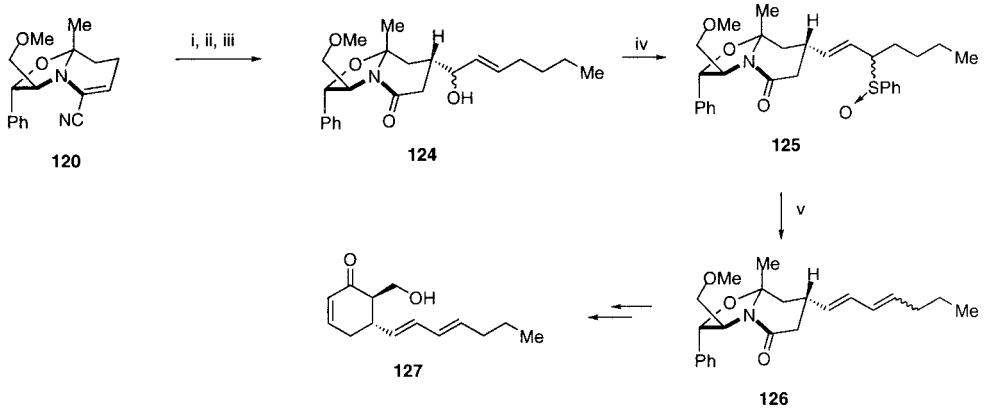
This sequence was employed to construct a variety of carbocycles including the major constituent of iris essential oil **128**,[37] the 'Woodward ketone' **129** (Fig. 14)[38] and (−)-penienone **127** (Scheme 26).[39]

In the (−)-penienone synthesis, the key transformation was the addition of *trans*-2-heptenal to the cyano-enamine **120** which afforded the requisite seven carbon side chain in **124** as a single diastereomer (*endo*). Subsequent [3,2] rearrangement of the sulfoxide in **125** and elimination gave **126** which produced penienone, **127** after hydrolysis, cyclization and hydroxymethylation.

Cyanoenamine alkylations were reported to construct the 2,4-*cis* disubstituted piperidines **132** by using the phenylglycinol based auxiliary.[40] Alkylation, followed by hydrolysis, gave lactam **130** (Scheme 27), which was reduced to the bicyclic oxazolidine **131**. Hydrogenolysis of the auxiliary produced the piperidine **132** as a single diastereomer.

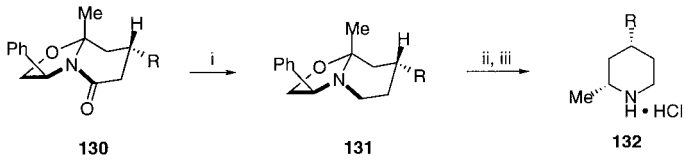
5.2. 2,6-Disubstituted piperidines

Thiolactams (e.g. **133**) were also utilized to access the 2,6-disubstituted *cis*-piperidines **135** via the Eschenmoser contraction.[41] Thus, reaction of thio-lactam **133** with methyl



i. LiTMP, HMPA, THF, -78 °C; ii. *trans*-heptenal, -78 °C; iii. THF/HCl, 25 °C;
iv. PhSCl, Et_3N, THF, 25 °C; v. THF, 65 °C

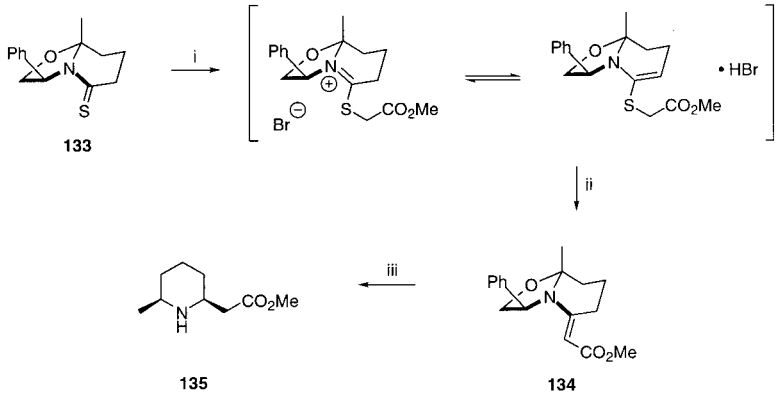
Scheme 26.



130 131 132

i. Red-Al; ii. $Pd(OH)_2$, H_2, MeOH; iii. HCl

Scheme 27.



133 135 134

i. 2-bromomethylacetate, triethylamine; ii. $P(OMe)_3$; iii. $Pd(OH)_2$, H_2

Scheme 28.

α-bromoacetate in the presence of trimethylphosphite furnished the vinylogous urethane **134** which was easily reduced to the piperidine, **135** (Scheme 28).[41]

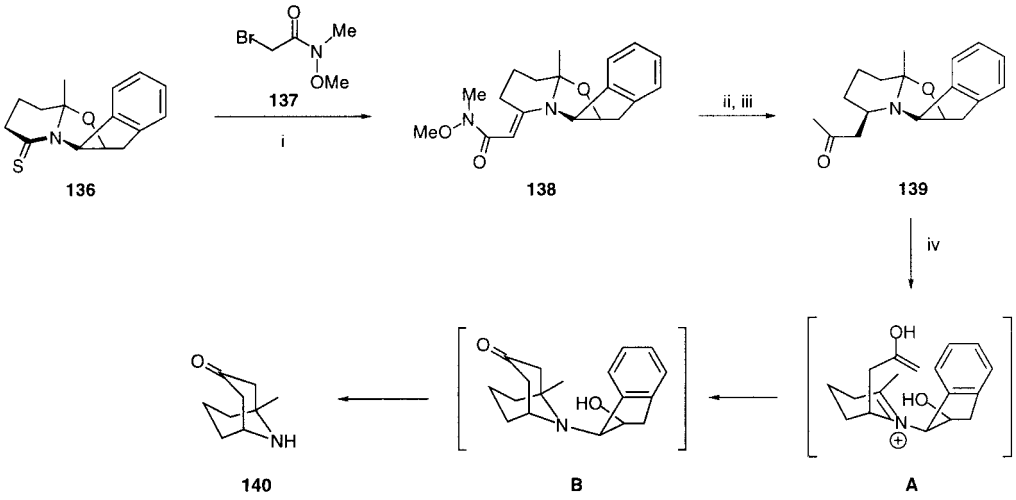
A variation of this sequence was employed in tandem with an intramolecular Mannich reaction to reach the homotropane (+)-euphococcinine, **140** (Scheme 29).[42] The Weinreb amide **137**[43] was simultaneously introduced into the thio-lactam **136** to afford the vinylogous urea **138**. Addition of methyl lithium provided the keto-oxazolidine **139** which was directly converted to the homotropane **140** via intramolecular Mannich cyclization, and passing through unisolated intermediates A and B.

6. Chiral Ketones

Although there are known routes[44] to chiral nonracemic ring systems represented by **141**, **142**, and **143** (Fig. 15), the bicyclic lactam has also provided an efficient general entry into these bicyclic systems.

6.1. Hydrinden-2-ones: synthesis of the core to (+)-magellanine

One of the key useful chemical features of the bicyclic lactam is the ketonic nature of the lactam carbonyl. Given the unexpectedly high electrophilic nature of the carbonyl,



136 138 139 140 B A

i. triethylamine, $P(OMe)_3$; ii. H_2, Pt/C; iii. MeLi; iv. NH_4OAc, HOAc.

Scheme 29.

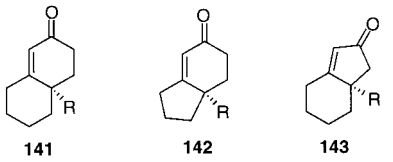


Figure 15.

intramolecular nucleophilic addition to this center produces the intermediate carbinolamine **144** which was converted, after hydrolysis, to the corresponding hydrinden-2-one, **143** (Scheme 30).[45]

This sequence was employed to construct the tetracyclic carbon skeleton **147** of the *Lycopodium* alkaloid Magellanine containing all six required contiguous stereogenic centers.[46] The key transformation in this sequence was the intramolecular addition of the alkyllithium derived from **145** to the bicyclic lactam carbonyl to access the appropriately substituted hydrinden-2-one **146**. Subsequent synthetic manipulations led ultimately to the tetracyclic system **147** (Scheme 31).

6.2. 5,5-Disubstituted 2-cyclopentenones

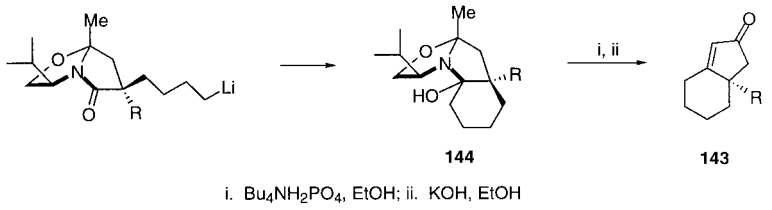
In addition to constructing the bicyclic system of hydrindenones, heavily substituted cyclopentenones **148** with different substitution patterns were also obtained by addition of alkyl lithiums to the electrophilic carbonyl present in bicyclic lactams (Scheme 32).[47] Following hydrolysis and base catalyzed aldol cyclization the trisubstituted cyclopentenones **148**, possessing a stereogenic quaternary center, were obtained.

6.3. Addition of vinyl anions to bicyclic lactams

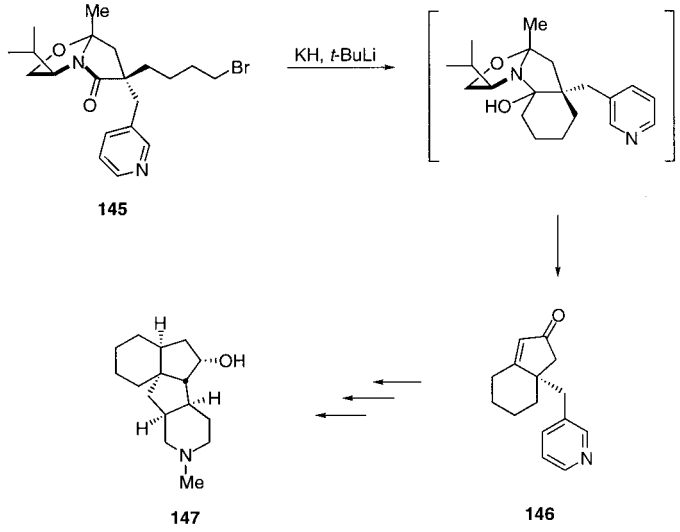
Through 1998, all the carbanions that had been added to the bicyclic lactam carbonyl were derived from sp^3 alkyl halides.

The addition of sp^2 anions (e.g. from β-bromostyrene) to the α,α-disubstituted bicyclic lactam **149** furnished cyclohexenone **150** after hydrolysis (Scheme 33).

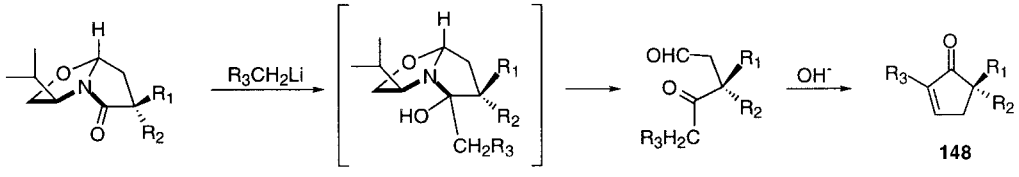
This process was applied toward a highly convergent total synthesis of trisporol B (Scheme 34, **154**).[48]



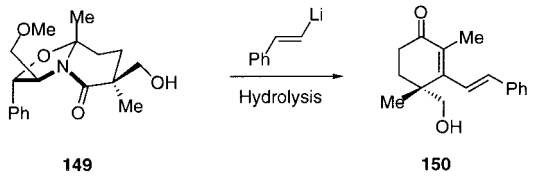
Scheme 30.



Scheme 31.

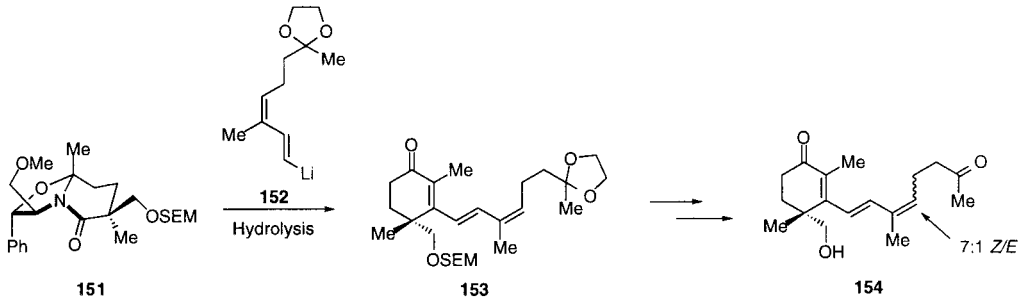


Scheme 32.



149 150

Scheme 33.



151 153 154

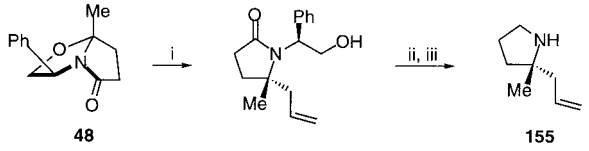
Scheme 34.

Addition of the vinyl anion **152** to the SEM-containing lactam **151** afforded the protected trisporol **153** in excellent yield as a single olefin diastereomer. During attempts to remove the protecting group an inseparable mixtures of olefin isomers **154** resulted.

7. Asymmetric Construction of Alkaloids

7.1. Pyrrolidines

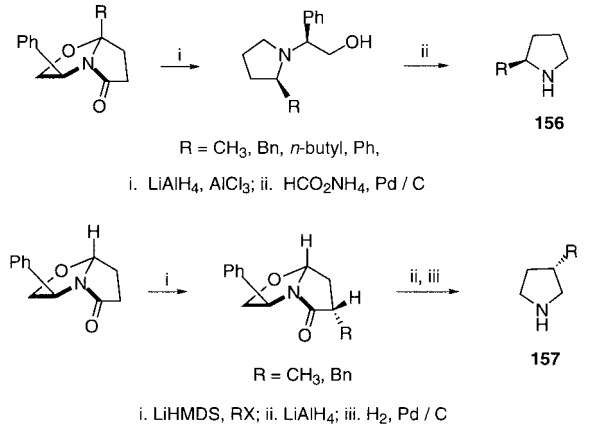
The addition of allylsilane to the angular position in the [3.3.0] bicyclic lactam **48** followed by two successive reductions furnished the conversion to a 2,2-disubstituted pyrrolidine **155** (Scheme 35).[49b]



48 155

i. allyltrimethylsilane, $TiCl_4$, CH_2Cl_2; ii. Li, NH_3, EtOH; iii. $LiAlH_4$

Scheme 35.



156 157

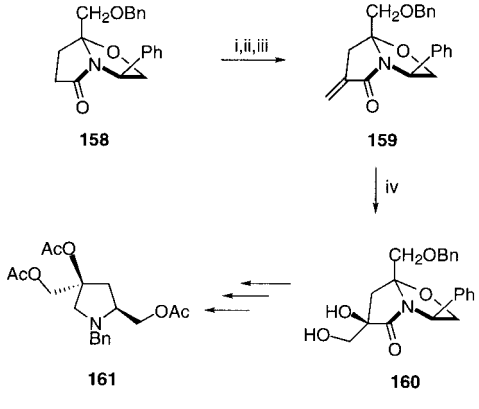
Scheme 36.

This work was followed by the construction of enantiomerically pure 2- and 3- monosubstituted pyrrolidines **156** and **157** by reduction of angular alkyl or monoalkylated bicyclic lactams respectively (Scheme 36).[50]

Polyhydroxylated pyrrolidines have been implicated in a variety of biologically important processes as a result of their ability to mimic carbohydrates. The [3.3.0] bicyclic lactam was employed as a template from which these optically pure compounds could be constructed (Scheme 37). Bicyclic lactam **158** was phosphonylated in the α-position followed by condensation with formaldehyde to afford the α-methylene derivative, **159**. Treatment of the latter with osmium tetroxide gave the vicinal diol **160** as a 7:1 diastereomeric mixture which was reductively cleaved. Protection of the resulting triol **160** as the peracetate furnished pyrrolidine **161** in excellent overall yield. It appears that the rigid [3.3.0] bicyclic lactam template possessed sufficient diastereoselective bias in the approach of the osmium to the *exo* methylene to afford the selectivity observed.[51]

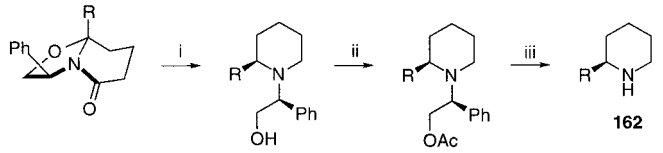
7.2. Piperidines

The above route to asymmetric pyrrolidines was extended to the piperidine series by use of the [4.3.0] bicyclic lactam,



158 159 160 161

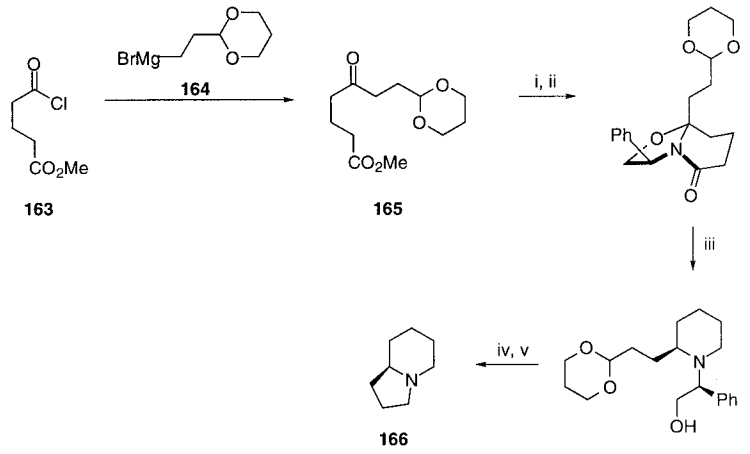
Scheme 37.



R = Me, *n*-Pr

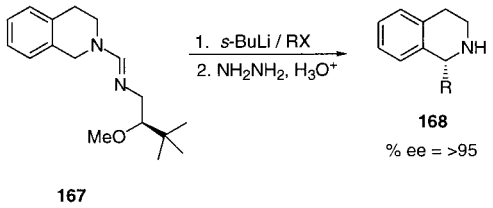
i. Red-Al, THF, Δ; ii. Ac_2O, DMAP, CH_2Cl_2; iii. $Pd(OH)_2$ / H_2

Scheme 38.



i. KOH; ii. (S)-phenylglycinol; iii. Red-Al; iv. HCl, THF, Δ; v. Pd / C, H_2

Scheme 39.



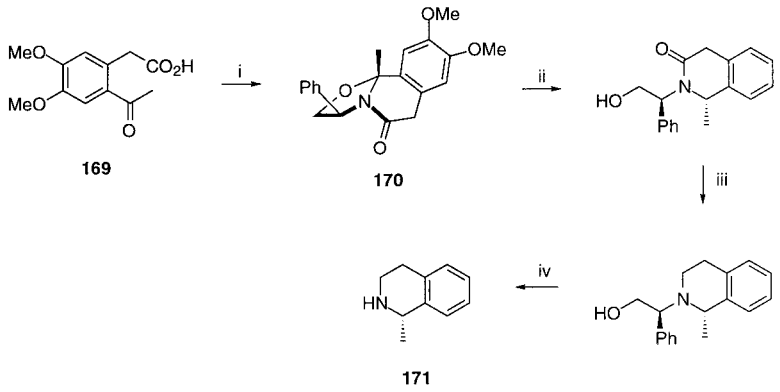
Scheme 40.

offering a general and efficient route to a variety of piperidine deriviatives **162** (Scheme 38).[52]

In order to make this route more general, an efficient procedure for constructing a variety of keto acids was developed. Thus, treatment of the commercially available acid chloride **163** with Grignard reagent **164** gave the desired keto ester (e.g. **165**). (−)-Coniceine **166**[52] was synthesized in three steps using this methodology which further demonstrated the synthetic utility of the appropriately substituted bicyclic lactam in alkaloid synthesis (Scheme 39).

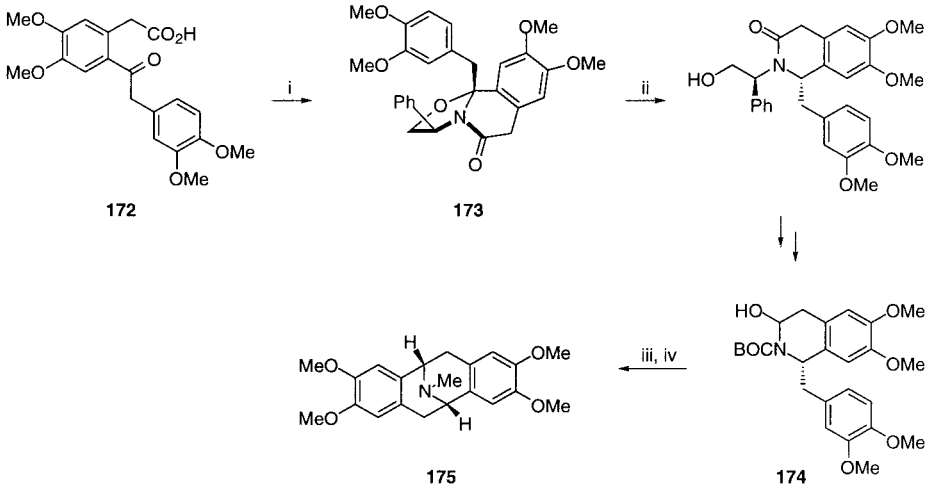
7.3. Tetrahydroisoquinolines

The chiral bicyclic lactam and its reductive cleavage to *N*-heterocycles was also applied to the efficient construction of tetrahydroisoquinoline alkaloids **168** (Scheme 40).[53] Tetrahydroisoquinoline alkaloids **168** had previously been synthesized in these laboratories in enantiomerically pure form using the formamidine **167**[54] as a directing group



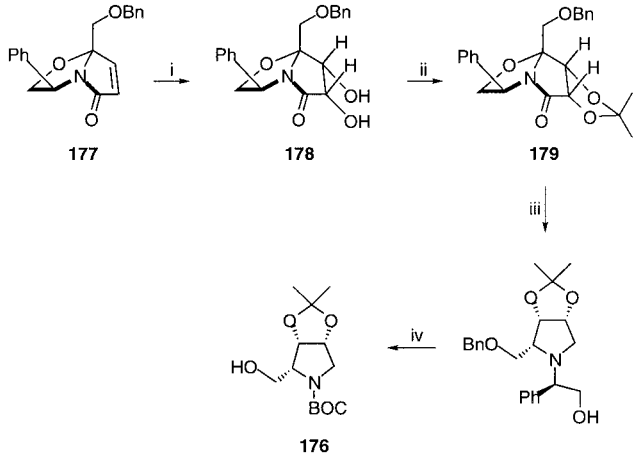
i. (S)-phenylglycinol; ii. Red-Al; iii. $LiAlH_4$; iv. Pd / C, H_2

Scheme 41.



i. (*S*)-phenylglycinol; ii. Red-Al; iii. TBSOTf, CH_2Cl_2; iv. H_2CO, $NaBH_4$

Scheme 42.



i. NMO, cat. OsO_4; ii. dimethoxypropane; iii. 9-BBN; iv. H_2 / BOC_2O, $Pd(OH)_2$

Scheme 43.

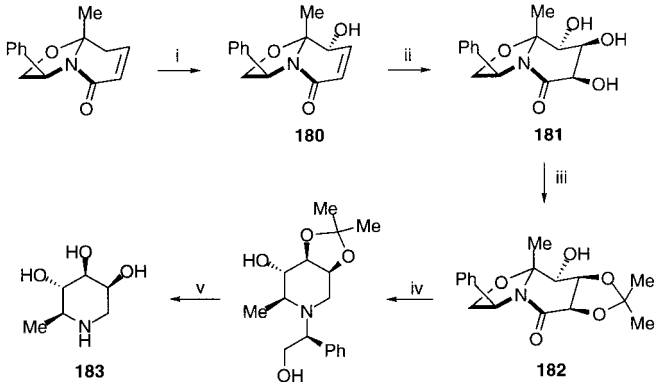
for the diastereoselective alkylation of a tetrahydroisoquinoline.

Similarly substituted tetrahydroisoquinolines were also obtained using the appropriately benzo-fused bicylic lactams **170**, following the reduction protocol previously described for the piperidine formation. The simple *ortho*-acylphenylacetic acid **169** was condensed with phenylglycinol and reduced to give (−)-salsolidine **171**[55] in three steps with high selectivity (Scheme 41).

This sequence was further employed in the asymmetric synthesis of 1,3-disubstituted tetrahydroisoquinolines and the first asymmetric route of (−)-argemonine **175** (Scheme 42).[56] The key transformation was exhibited by the diastereoselective intramolecular Pictet–Spengler cyclization of the carbinolamine **174**.

7.4. Azasugars

Azasugars, an important class of biologically active targets, have also been synthesized in a rapid and efficient manner by using the bicyclic lactam template.[57] These laboratories



i. SeO_2, dioxane; ii. OsO_4 / NMO; iii. $(CH_3)_2C(OMe)_2$, CH_2Cl_2, pTSA; iv. BH_3•THF; v. H_2 / Pd, MeOH, then TFA

Scheme 44.

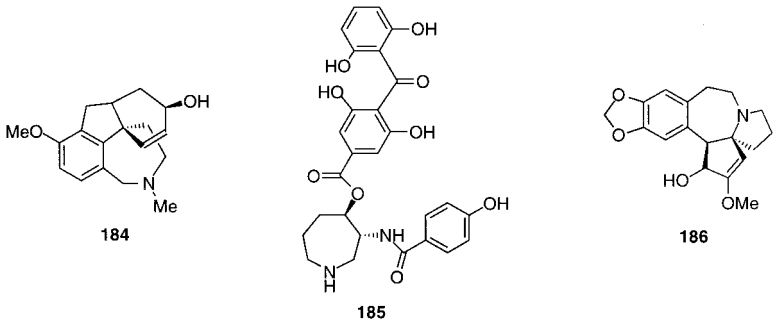


Figure 16.

first investigated the use of the [3.3.0] bicyclic lactam in the formal synthesis of 1,4-dideoxy-1-4-imino-D-lyxitol **176** (Scheme 43).[58] Dihydroxylation of the α,β-unsaturated bicyclic lactam **177** produced the diol **178** as a 7:1 mixture of diastereomers. This was protected as its acetonide **179** to provide an additional 'steric control element', which aided in the stereoselective reduction of the angular position. This general method afforded nonracemic azasugars from non-sugar starting materials, offering the ability to construct a wide variety of structural derivatives.

A similar approach was also taken to achieve the synthesis of L-*rhamno*-1-deoxynojirimycin **183** (Scheme 44), as well as other piperidine based derivatives.[59] Oxidation of the α,β-unsaturated lactam with selenium dioxide surprisingly furnished the allylic alcohol **180** as a single diastereomer. The angular alkyl group present in the lactam appears to have been responsible for this strong steric effect, which directed the oxidation in an *anti* fashion. Once the allylic hydroxyl was in place, the subsequent dihydroxylation to **181** occured with complete stereocontrol. This observation, previously discussed by Kishi,[60] wherein the oxidation proceeds *anti* to an allylic hydroxyl group appears to be due to the donation of electrons from the C–O σ bond to the π^* of the olefin.

7.5. Chiral non-racemic [5.3.0] bicyclic lactams. Synthesis of perhydro- and benzo-fused azepines

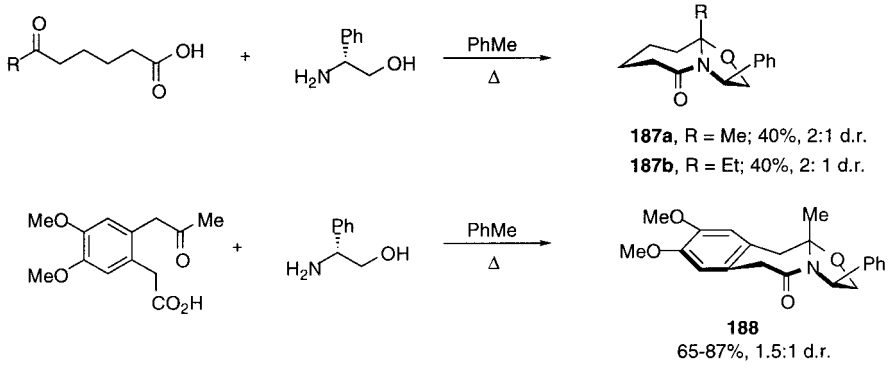
Azepines are constituents in a variety of compounds with interesting pharmacological properties,[61] i.e. galanthamine[62] **184** (analgesic properties), cephalotaxane[63] **186** (antileukemia) and balanol[64] **185** (protein kinase C inhibitor) (Fig. 16). Construction of a [5.3.0] bicyclic lactam presented a reasonable template for the synthesis of this important class of alkaloids. The two effective routes developed to access these bicyclic lactams were the usual cyclodehydration of a keto-acid containing a conformational constraint in its backbone or via ring closing metathesis[65] of the appropriately substituted *N*-acyl oxazolidine.

Unfortunately, cyclodehydration afforded the angular methyl **187a**, ethyl **187b** and benzofused **188** [5.3.0] bicyclic lactams in low diastereoselectivity (Scheme 45). These lactams (after separation via chromatography) were stereoselectively reduced to furnish 2-substituted perhydroazepines (**190**, **191**) with good enantiomeric excess (84–94%).[66] The rationale for the high selectivity was similar to that in past reductions of the [4.3.0] and [3.3.0] bicyclic lactam systems.[49] Thus, coordination of aluminum to the oxazolidine oxygen with concomitant delivery of the hydride to the *N*,*O*-acetal, furnished the monocyclic azepine **189** with retention of stereochemistry (Scheme 46).

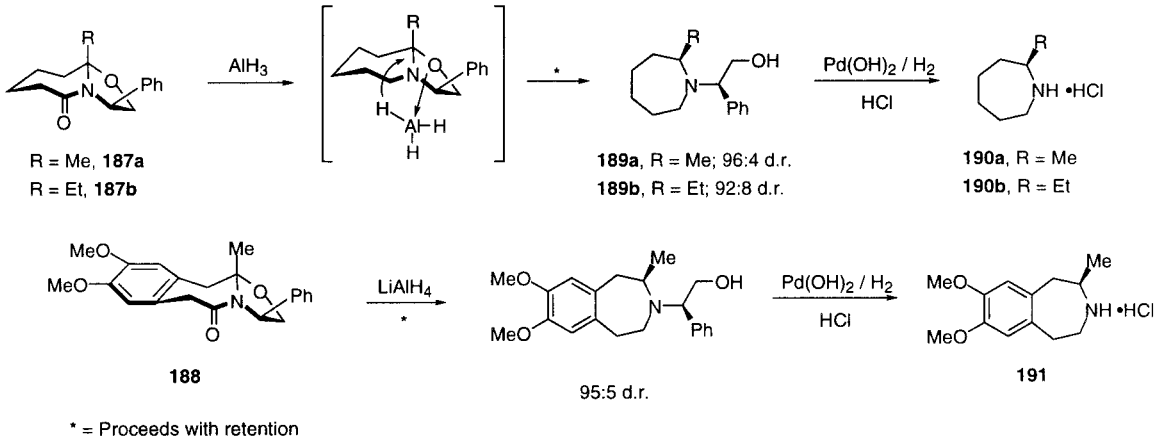
The ring closing metathesis process was employed to access the α,β-unsaturated [5.3.0] bicyclic lactam **194** (Scheme 47).[66b] Routine formation of the oxazolidine ring **192** was followed by acylation and separation of the 3:1 diastereomeric mixture of acrylamides **193**. Ring closing metathesis and reduction of **194** then gave the desired bicyclic lactam **187a** in good overall yield (>60% yield).

7.6. Trifluoromethyl-substituted piperidines and decahydroquinolines

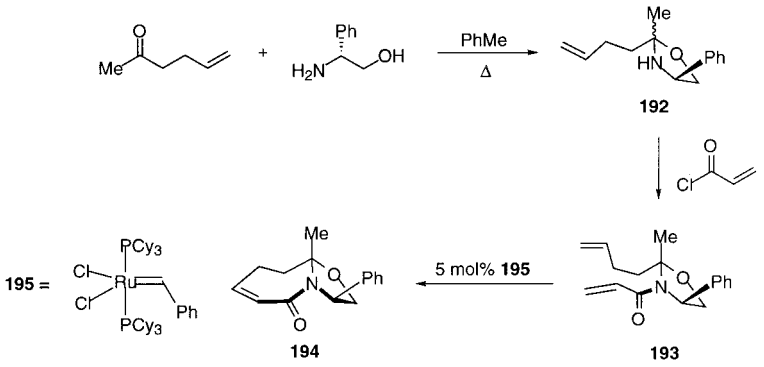
The incorporation of the trifluoromethyl group in the bicyclic lactam system imparts dramatic effects on



Scheme 45.

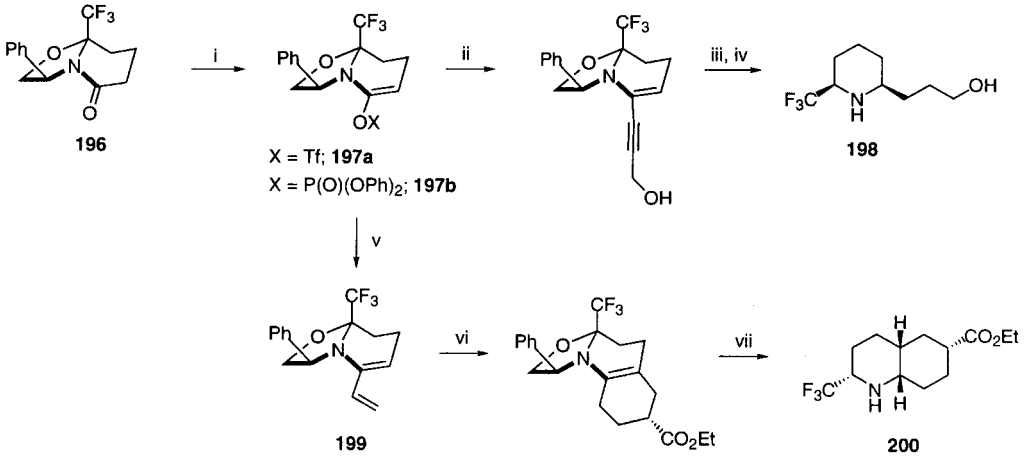


Scheme 46.



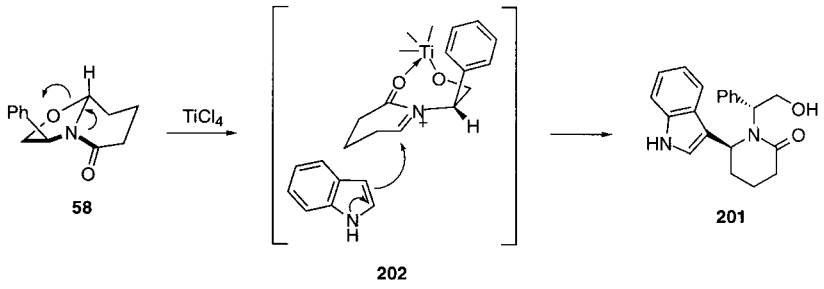
Scheme 47.

subsequent chemical transformations.[67] Contrary to the chemistry performed on the perhydro–lactam, the enolate of the trifluoromethyl substituted bicyclic lactam **196** was trapped with the Commins reagent[68] to afford the vinyl triflate **197a** (Scheme 48). A variety of transition metal catalyzed reactions were reported to occur with this substrate to give trifluoromethyl substituted piperidines **198**.[69] Conversion of the vinyl phosphate **197b** to the diene **199** was followed by Diels–Alder cycloaddition to give decahydroquinolines **200**.

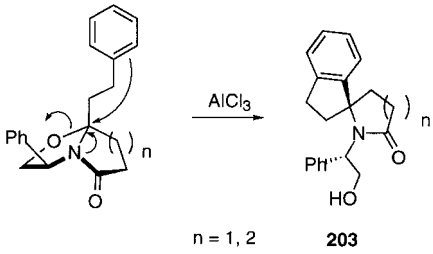


i. **197a**: KHMDS, N-(5-chloro-2-pyridinyl)triflimide; **197b**: KHMDS, $(PhO)_2P(O)Cl$;
ii. propargyl alcohol, $PdCl_2(PPh_3)_2$, CuI; iii. PtO_2 / H_2, toluene; iv. $Pd(OH)_2$ / H_2, EtOH;
v. tributyl(vinyl)tin, LiCl, $Pd(PPh_3)_4$; vi. ethylacrylate; vii. $Pd(OH)_2$ / H_2, EtOH

Scheme 48.



Scheme 49.



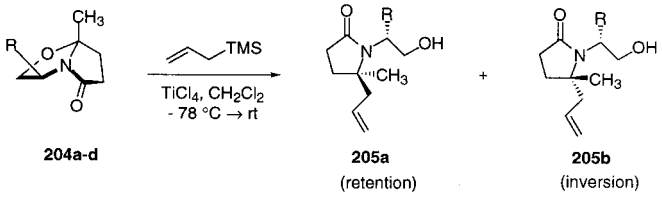
Scheme 50.

8. Additions to *N*-Acyliminium Ions

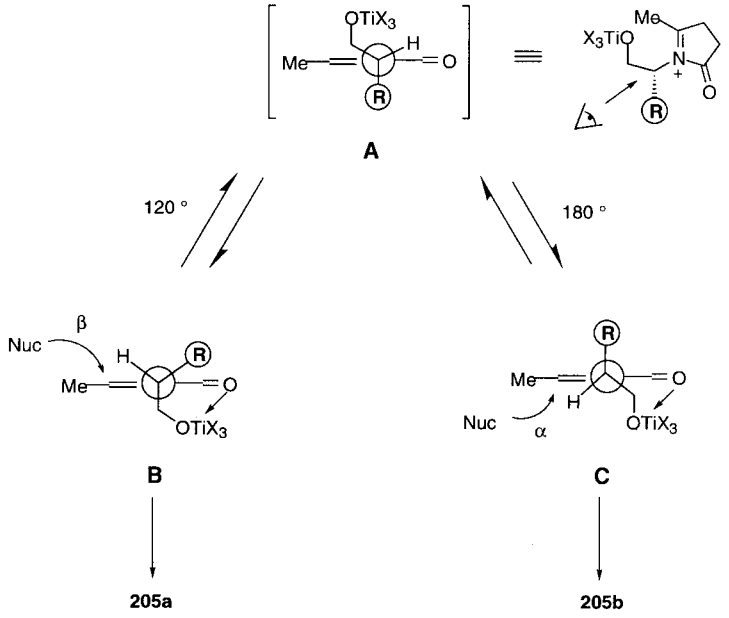
8.1. Friedel–Crafts additions

The *N*,*O*-acetal carbon of the bicyclic lactam can function as an electrophilic center upon treatment with a strong Lewis acid. The electrophilic nature of this carbon was exploited by addition of various nucleophiles. For example, when bicyclic lactam **58** was treated with an equivalent of titanium tetrachloride in the presence of indole, 6-indoyl-2-piperidones **201** were formed.[70] The stereochemical

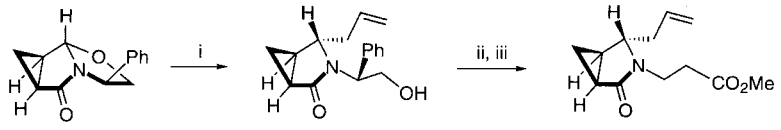
Table 9. Allylsilane additions to **204a–d**



204	R	d.r. (**205a: 205b**)
a	methyl	8:1
b	phenyl	5:1
c	*iso*-propyl	1:2
d	*tert*-butyl	1:11



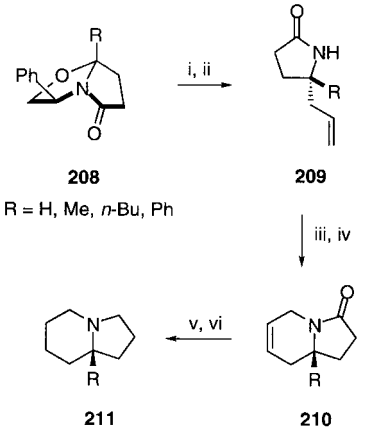
Scheme 51.



206 (+)-207

i. allyltrimethylsilane, $TiCl_4$; ii. Ca / NH_3; iii. KH, 3-bromo methyl propionate

Scheme 52.



208 209 211 210

R = H, Me, *n*-Bu, Ph

i. allyltrimethylsilane, $TiCl_4$; ii. Ca / NH_3; iii. NaH / allylbromide
iv. $(PCy_3)RuCl_2(CHPh)$ 10 mol%.; v. H_2 / $Pd(OH)_2$; vi. $LiAlH_4$

Scheme 53.

rationale was based upon a chelation control model as illustrated in **202** (Scheme 49).

An intramolecular variant of this Mannich-type reaction has also been performed. An aryl group tethered to the angular position reacted in the presence of a Lewis acid to afford spiropyrrolidinones and piperidones **203** (Scheme 50).[71]

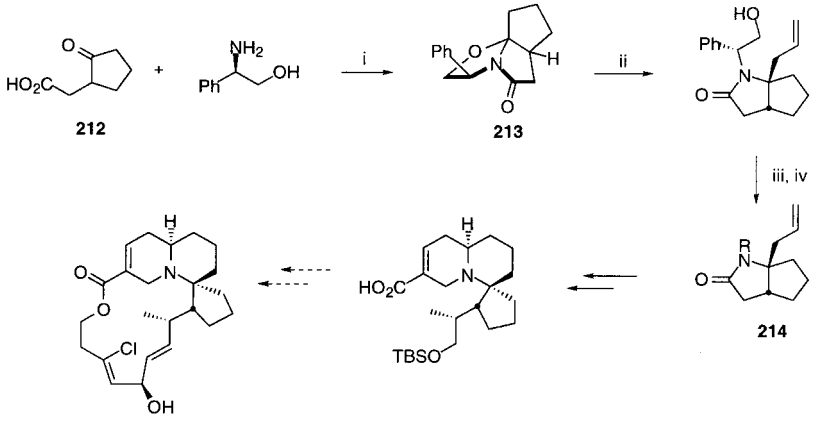
8.2. Allylsilanes additions

Most of the work regarding additions to an *N*-acyl iminium ion have been focused on the additions of allylsilanes (Table 9). These additions to a bicyclic lactam disclosed an interesting stereochemical trend.[49a] The stereochemistry of the Lewis-acid mediated allylsilane alkylation could be controlled by changing the nature of the auxiliary group from small (methyl) to large (*tert*-butyl).

An explanation was proposed for the stereochemical outcome observed for **205a/205b** (Scheme 51). A model was based upon a combination of the Felkin–Ahn model, allylic 1,3-strain and chelation effects. The initially formed *N*-acyliminium ion **A**, is capable of bond rotation. Allylic 1,3-strain would force a rotation to either 120 or 180° to minimize conjestion around the olefinic center. From the model of Felkin–Ahn, **C**, entry by the allylsilane would occur from the face opposite the large group to generate the product (α-entry) of inversion **205b**.

Alternatively, the alkoxytitanium moiety assumes the role of the large group, occupies the gauche position (**B**), thus directing a β-entry to generate the product of retention **205a**. Finally, and perhaps of equal significance, the existence of a seven-membered-ring chelate in **B** and **C** derived from the alkoxytitanium and the carbonyl oxygen could impart added preference for either outcome.

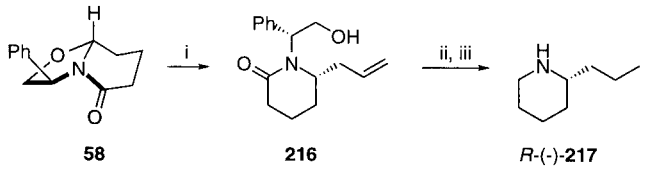
This process of reductive ring cleavage was utilized in the asymmetric construction of the bicyclic precursor to (−)-indolizomycin **207** (Scheme 52).[72] The key transformation was the addition of allyltrimethylsilane to the cyclopropyl lactam **206** which occurred with complete stereocontrol at the reacting center.



212 213 214 215

i. PhMe, Δ; ii. allyltrimethylsilane, $TiCl_4$; iii. (R = H) Na, NH_3; iv. Boc_2O, DMAP.

Scheme 54.



i. allyltrimethylsilane, $TiCl_4$; ii. $LiAlH_4$; iii. H_2 / Pd-C

Scheme 55.

A general route to indolizidines was developed from this methodology and applied to the synthesis of (−)-coniceine **211** (Scheme 53).[73] Allyltrimethylsilane was added to a variety of bicyclic lactams **208** in the presence of Lewis acids. Reductive cleavage of the benzylic carbon–nitrogen bond gave the 5-allyl pyrrolidinone **209**. Addition of allylbromide to the amide nitrogen followed by ring closing metathesis furnished the 1-azabicyclo[4.3.0]nonenones **210**. Reduction of the amide carbonyl and double bond yielded the indolizidines **211** in an efficient manner.

Danishefsky[74] employed this method in his asymmetric construction of spiroquinolizidine subunit **215** of halichlorine (Scheme 54). Condensation of the keto acid **212** with (−)-phenylglycinol followed by Lewis acid mediated addition of allyltrimethylsilane and reductive removal of the auxiliary gave the pyrrolidinone **214**, which was converted to **215** after a number of synthetic steps.

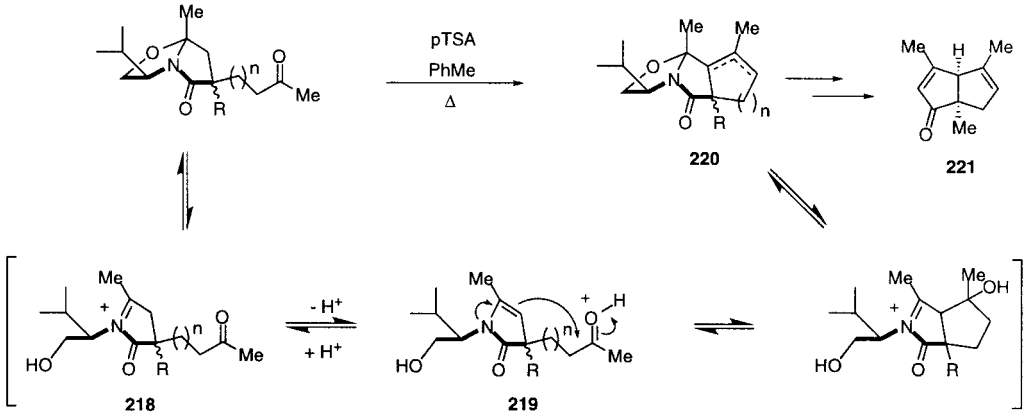
Using the [4.3.0] bicyclic lactam, a similar sequence was utilized to construct the piperidine alkaloid (−)-coniine.[75] Addition of allyltrimethylsilane to the [4.3.0] bicyclic lactam **58** afforded a >9:1 mixture of diastereomeric 6-allyl piperidone **216**. The mixture was separated and ultimately converted to *R*-(−)-coniine **217** (Scheme 55).

Another pathway was uncovered which appeared to proceed through equilibration of the acyliminium ion **218** with the acyl-enamide **219** (Scheme 56).[76] This novel process was responsible for cyclization to the tricylic lactam **220** which was converted to the bicyclic [3.3.0] octenone **221**.

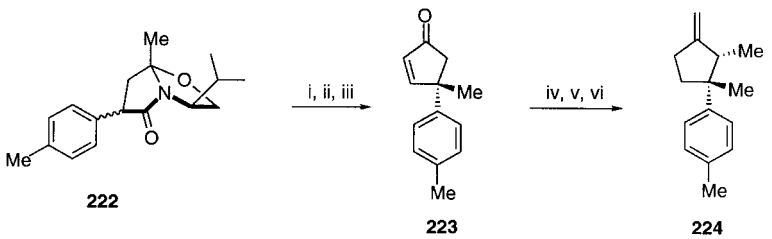
9. Synthesis of Complex Enantiomerically Pure Compounds

9.1. (+)-Laurene

The bicyclic lactam system has been employed to construct (+)-laurene **224**[77] which possesses the synthetically challenging vicinal tertiary and quaternary centers (Scheme 57). The inconsequential mixture of α-aryl bicyclic lactams **222** was alkylated in >95:5 (*endo*:*exo*) diastereomeric ratio and converted to the optically pure cyclopentenone **223**. The latter was alkylated with methyl iodide to afford an epimeric mixture(8:1) at the tertiary stereogenic center. Methylenation of the carbonyl using



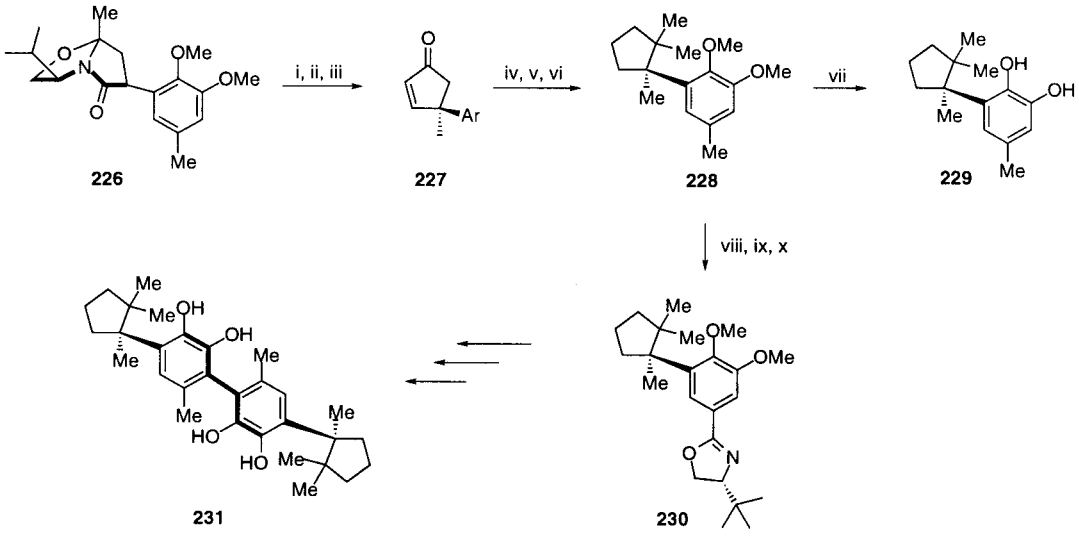
Scheme 56.



i. LDA, MeI; ii. Red-Al; iii. $Bu_4NH_2PO_4$, followed by KOH;
iv. LDA, MeI; v. H_2, Pd / C; vi. **225**

225 = $Cp_2Ti(CH_2)(Cl)AlMe_2$

Scheme 57.



i. LDA, MeI; ii. Red-Al; iii. a. NaH_2PO_4, b. NaOH; iv. NaH, MeI; v. $(ArPS_2)_2$; vi. Raney Ni, H_2; vii. BBr_3; viii. Br_2, CH_2Cl_2; ix. $Co(OAc)_2$, O_2; x. a. $(COCl)_2$, b. *tert*-leucinol, c. $SOCl_2$, d. K_2CO_3

Scheme 58.

Tebbe's reagent **225** gave laurene with no erosion of the 8:1 epimeric mixture of **224**.

9.2. (−)-Herbertenediol and (−)-mastigophorene A and B

A similar alkylation strategy as described above was used to construct the cyclopentane natural product herbertenediol **229** and its two dimeric atropisomers mastigophorenes A and B **231** (Scheme 58).[78] The featured step in this transformation was the construction of a quaternary stereogenic center with complete sterecontrol. Alkylation of the mixture of α-aryl bicylic lactams **226** afforded the single quaternary stereocenter in the cyclopentane core **227** after reduction and hydrolytic cleavage. The cyclopentane was subsequently converted to cyclopentane **228** containing the required vicinal quaternary centers. Methoxyl cleavage led to herbertenediol **229**, whereas transformation of **228** to the aryl-oxazoline **230** led to each of the atropisomers of **231** after asymmetric aryl–aryl coupling.[79]

9.3. The core cyclopentane of viridenomycin

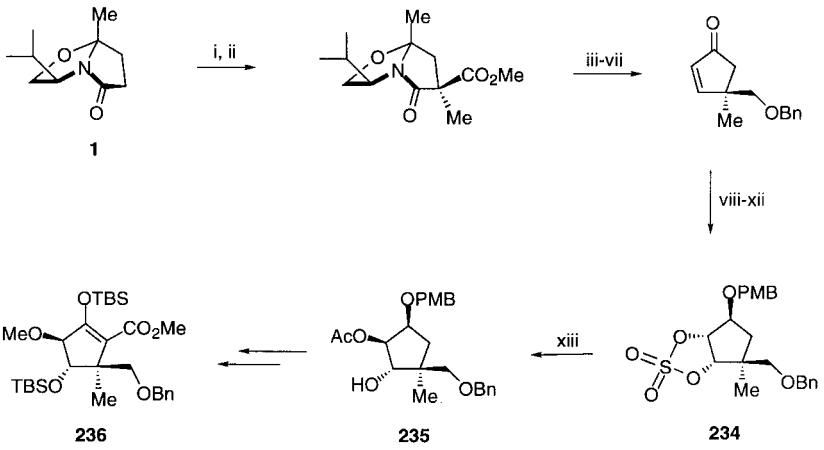
Continued efforts to apply the bicyclic lactam template to the construction of optically pure carbocycles and heterocycles opened a route to the highly oxygenated cyclopentane core (**232**) of viridenomycin **233** (Fig. 17).[80]

The cyclopentenone equivalent **232** was reached by alkylation of the [3.3.0] bicyclic lactam **1** with methyl iodide followed by acylation with methylchloroformate (Scheme 59). Interestingly, the *acylation* proceeded with *complete exo selectivity*. This trend of sp^2 hybridized electrophiles approaching the enolate of **1** with high *exo*-selectivity has been observed in other systems.[48] The origin of this reversal in diastereofacial selectivity remains an unanswered question although initial *O*-acylation should be considered. The introduction of the *trans* diol moiety in the cyclopentenone, was accomplished by formation of the cyclic sulfate **234** followed by opening with cesium acetate. This afforded the *trans* diol **235** which was then converted to the cyclopentene derivative **236**, a close, useful precursor to **232**.

9.4. The hydroindolone core of amaryllidaceae alkaloids

Using similar sequences as those employed in the synthesis of mesembine,[81] the core (**241**) of the amaryllidaceae alkaloids was constructed (Scheme 60).[82] The requisite keto acid **237** was condensed with the amino propanediol to afford a mixture of diastereomers of the [4.3.0] bicyclic lactams **238**. Alkylation with acrolein and protection yielded **239** as a single diastereomer at the α-position (1:1 mixture at the allylic center). Pappo–Johnson[83] oxidation, followed by reductive amination, afforded the protected amino alcohol **240** which was converted to the hydroindolone **241**, the

Figure 17.



i. LDA, MeI; ii. LDA, $ClCO_2Me$; iii. $NaBH_4$; iv. NaH, BnCl; v. Red-Al;
vi. $NBu_4H_2PO_4$; vii. KOH, THF;viii. DIBALH; ix. KH, PMBCl;
x. $K_2OsO_4{\bullet}H_2O$, NMO; xi. $SOCl_2$, Et_3N; xii. $RuCl_3{\bullet}H_2O$, $NaIO_4$; xiii. a. CsOAc, b. H_2SO_4

Scheme 59.

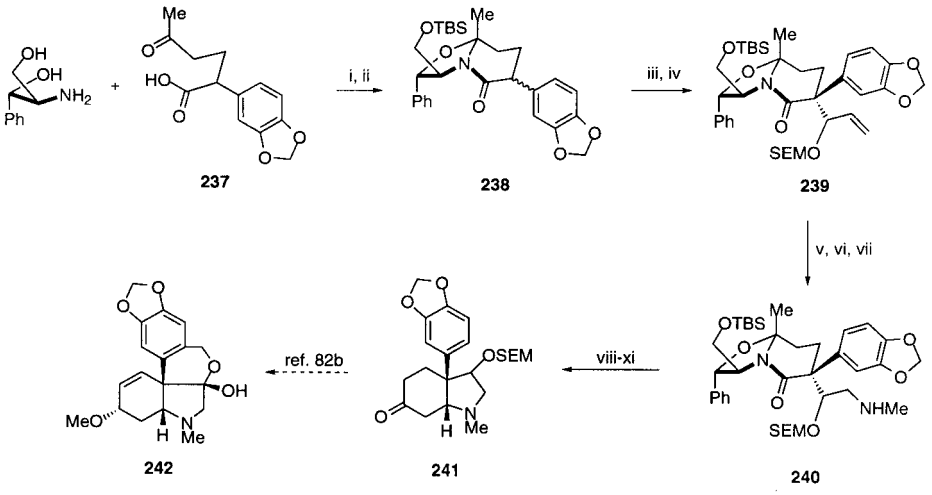
latter of which, is known to furnish the amaryllidaceae alkaloids.[82b]

9.5. Zizaene

The simple bicyclic lactam **1** was utilized along with the ring closing metathesis reaction to access the core of the tricyclic sesquiterpene zizaene, **249** (Scheme 61).[84] Sequential alkylation of **1** furnished the bis-olefin **243** which was subjected to the ring closing metathesis conditions yielding the spiro product **244**. Reduction of the olefin was followed by the reduction/hydrolysis/aldol sequence to give the spirocyclopentenone **245**. Cyclopentane **246** was subjected to acid catalyzed intramolecular aldol conditions to afford the tricyclic core of zizaene **247**. Transposition of the carbonyl intercepted the advanced intermediate **248** reported by Coates' [85] in the racemic synthesis of zizaene.

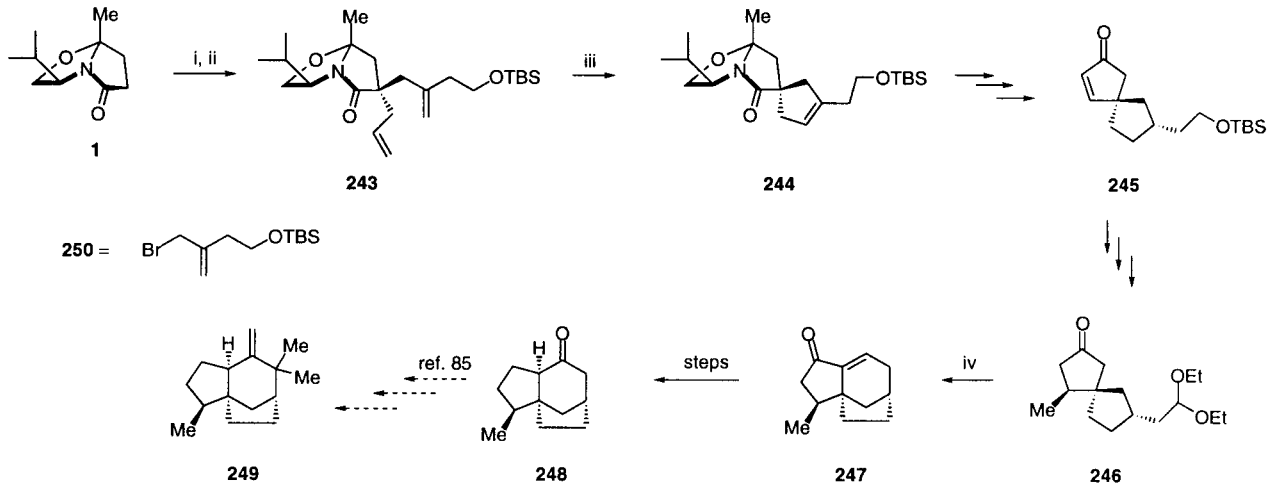
10. Summary

The chiral non-racemic bicyclic lactam has proven to be an exceptionally versatile chiral template for the asymmetric construction of a variety of optically pure compounds. Those lactams derived from keto acids have been applied to the synthesis of a host of natural products and pharmacologically interesting heterocycles and carbocycles. A variety of mechanistic questions regarding facial stereocontrol have been investigated using the chiral template as the key probe. However, further elucidation of the subtle mechanistic principles involved await further study.



i. PhMe, Δ; ii. TBSCl, imid.; iii. LDA, acrolein; iv. SEMCl, $^iPr_2NEt$; v. OsO_4 (cat), NMO;
vi. $NaIO_4$; vii. $MeNH_2$, $NaCNBH_3$; viii. TBAF; ix. RedAl; x. $Bu_4NH_2PO_4$; xi. NaOH.

Scheme 60.



i. LDA , **250**; ii. LDA, allylbromide; iii. Grubbs' cat. (5 mol%); iv.TsOH.

Scheme 61.

Acknowledgements

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Biographical Sketch

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